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Relationship between clinical variables, quality of life and fatigue in patients with multiple myeloma.

by

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Dedication

This thesis is dedicated to the amazing individuals who graciously participated in this study. Your courage, dignity and strength have been inspiring. Thank you.

Abstract

Fatigue is one of the most commonly reported symptoms in patients with cancer and is almost certain to occur at some point along the illness trajectory in patients with multiple myeloma. Fatigue is a multifaceted symptom whose etiology remains unknown. Most research has focused on the role of anemia however there is growing evidence that other processes, such as inflammation, may contribute to the development of fatigue.

This study employed a descriptive exploratory design. Fifty-six patients with multiple myeloma were accrued from an outpatient oncology clinic. Bivariate relationships were demonstrated between hemoglobin and fatigue ($r=-0.352$, $p=0.008$) and hemoglobin and QOL ($r=0.406$, $p=0.002$), CRP and fatigue ($r=0.503$, $p<0.00001$) and CRP and QOL ($r=-0.524$, $p<0.00001$). Of interest, multivariate regression analysis identified that CRP was a significant predictor of fatigue ($p=0.004$) and QOL ($p=0.010$), while hemoglobin was not predictive of fatigue ($p=0.28$) or QOL ($p=0.328$) once the effect of CRP was accounted for.

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Chapter 1: Introduction

Problem Statement

In Canada, an estimated 38% of women and 44% of men will receive a cancer diagnosis in their lifetime (Canadian Cancer Society/National Cancer Institute of Canada [CCS/NCIC], 2006). An approximate 2865 Canadians are diagnosed with cancer each week, with an overall prevalence of 2.4% of men and 2.7% of women. Multiple myeloma (MM) represented 1.2% of all new cases of cancer and 1.8% of all cancer deaths in 2006. This corresponds to 1900 new diagnoses of MM and 1300 deaths due to MM in 2006 (CCS/NCIC). A consequence of both the disease and the treatment, fatigue is a seemingly ubiquitous symptom that MM patients encounter along the illness trajectory.

Fatigue is a symptom with a constellation of possible etiological factors including physiological (such as anemia due to bleeding, hemolysis, nutritional deficiencies, cytokines, chemotherapy, radiotherapy), treatment (chemotherapy, biotherapy, hormonal therapy, radiotherapy), cachexia, tumor burden, cytokines and psychosocial factors (such as anxiety, depression, sleep disturbance, employment status, physical activity, unmanaged symptoms) (Ahlberg, Ekman, Gaston-Johansson & Mock, 2003). Fatigue in cancer has been described as being unlike fatigue associated with normal physical or mental exertion, with distinct physical, sensory, affective and cognitive components (Barnes & Bruera, 2002; Gutstein, 2001; Olson & Morse, 2005).

Fatigue invariably influences quality of life (QOL), with the literature reporting severe fatigue and QOL as being inversely related (Holzner et al., 2002; Knight, Wade & Balducci, 2004; Lind et al., 2002). Since QOL has been shown to be an independent predictor of survival (Brown, McMillan & Milroy, 2005; Chang et al., 1998; Earlam,

Glover, Fordy, Burke & Allen-Mersh, 1996; Wisloff & Hjorth, 1997), interventions that decrease fatigue may result in increased survival.

Purpose

The purpose of this study was to begin an investigation of factors related to disease and treatment in MM that contribute to the development of fatigue in these individuals. Fatigue remains a multifaceted symptom (Dimeo et al., 2004). Although most research has focused on the role of anemia, there is some evidence that other pathways related to the inflammatory process and tumor burden also influence the development of fatigue in this population. A greater understanding of the association between these clinical factors may provide valuable insight into the pathophysiology of fatigue in MM, provide important information about individual experience and lead to improved symptom management and quality of life in these individuals.

Objectives and Hypotheses

While researchers have examined clinical factors associated with cancer-related fatigue, none have expressly examined clinical correlates of fatigue in individuals with MM. Most research to date has focused on the association between hemoglobin and fatigue. However, the relationship between anemia and fatigue has not always been consistent and the degree of anemia is not always correlated with severity of fatigue (Morrow, Andrews, Hickok, Roscoe & Matteson, 2002). There is a growing body of evidence that suggests cytokines play a pivotal role in the development of cancer related symptoms such as pain, cachexia and fatigue. The hypothesis underlying this study was that anemia was not the sole predictor of fatigue in patients with multiple myeloma and

that proinflammatory cytokines play a role in the development of fatigue in this population. C-reactive protein (CRP) was used as a surrogate marker of inflammation. The objective of this study was:

> To examine the relationships between clinical variables (hemoglobin, C-reactive protein) fatigue and quality of life in individuals with MM.

These particular clinical variables were selected because they are readily available through routine blood work in this population. Hemoglobin was considered a marker for anemia and C-reactive protein was considered a marker for the inflammatory process.

Hypothesis:

> H0: Anemia is the exclusive predictor of both fatigue and quality of life in individuals diagnosed with MM.
>
> H1: Anemia is not the exclusive predictor of fatigue or quality of life in individuals diagnosed with MM.

Chapter 2: Literature Review

A comprehensive review of Medline (1966-May 2005), EMBASE (1980-May 2005) and CINAHL (1982-May 2005) was conducted. Search terms employed included: multiple myeloma, symptom distress, symptom burden, cancer related fatigue, cytokines and cancer related symptoms, cytokines and fatigue, fatigue and multiple myeloma, anemia and multiple myeloma, treatment of multiple myeloma, prognostic factors and multiple myeloma, quality of life and multiple myeloma. The above terms were searched individually and in various combinations. Reference lists from articles were manually searched for additional literature. English-language published papers that reported results

of randomized trials, meta-analyses, literature reviews were reviewed in preparation for this study.

Multiple Myeloma

Epidemiology

Multiple myeloma represents approximately 1% of all cancers and 10-15% of hematological malignancies (Joshua & Gibson, 2002; Kyle et al., 2003). It is a disease that affects more men than women at a 3:2 ratio (International Myeloma Foundation [IMF], 2004). The incidence of MM increases with age, with less than 2% of cases occurring before the age of 40 (Joshua & Gibson; Smith, Wisloff, & Samson, 2006). Overall survival rates range from several months to more than twenty years (Stead et al., 1999). Median survival has been reported as 33 months in one study (Kyle et al.), and Richardson (2003) reported a range of 3 to 5 years. Without treatment, survival is estimated to be approximately 6 months. The median survival of a patient with relapsed MM is 1 to 3 years. A diagnosis of refractory MM is associated with a median survival of 6 to 9 months. Survival rates are contingent upon an array of patient factors and disease characteristics (Joshua & Gibson, 2002).

Diagnostic criteria for symptomatic multiple myeloma.

A diagnosis of multiple myeloma is made upon detection of the presence of an M protein component in the serum and/or urine plus clonal plasma cells in the bone marrow and/or a documented clonal plasmacytoma AND one or more of the following, attributable to the underlying plasma cell disorder (Durie et al., 2006):

Calcium elevation (>2.65mmol/L)

Renal insufficiency (creatinine ≥177μmmol/L)

Anemia (hemoglobin <100g/L or 20g/L below normal)

Bone disease (lytic lesions or osteopenia)

An abnormal serum free light chain is an acceptable substitute in patients with no detectable M-component. Patients with normal serum free light chain ratio and no serum/urine M-component detectable may still be diagnosed with myeloma if they have ≥10% clonal plasma cells. This would be considered 'nonsecretory' multiple myeloma.

Prognostic Factors in Multiple Myeloma

Many researchers have examined variables for prognostic significance in MM with respect to both survival and response to treatment (Durie et al., 2003). Table 1 summarizes the recognized prognostic variables in myeloma.

Table 1. Recognized Prognostic Factors

Factor	Significance
Age	Younger → better
Performance status	Low levels → poor
β_2-microglobulin	High → poor
Serum albumin	Low → poor
Serum creatinine	High → poor
LDH	High → poor
C-reactive protein	High → poor
Hemoglobin	Low → poor

Platelet count	Low → poor

Table 1. Recognized Prognostic Factors (Durie et al., 2003)

Factor	Significance
Plasma cell labeling index	High → poor
Plasma cell morphology	Plasmablastic → poor
Chromosome 13	Hypodiploidy/deletion 13 → poor
Whole body FDG/PET scan	Extradmedullary disease → poor

Note. From "Myeloma management guidelines: A consensus report from the Scientific Advisors of the International Myeloma Foundation," by B.G. Durie et al., 2003, *The Hematology Journal, 4,* p. 379-398. Copyright 2003 by Ferrata Storti Foundation and Ediciones Doyma.

Staging

Up until recently, the most commonly used staging system for patients with MM was the Durie-Salmon (DS) system, which was introduced in 1975 (Greipp et al., 2005). The DS classification included the level and type of monoclonal protein, hemoglobin, calcium level and number of lytic bone lesions. Further stratification into high and low risk categories was based on serum creatinine level. The DS classification imparted important prognostic information in patients with MM. More recently, additional factors have been identified as being prognostically significant in patients with MM including serum β_2-microglobulin, albumin, C-reactive protein and plasma cell labeling index (Greipp et al.).

In 2005, Greipp et al. proposed a new staging system, the International Staging System (ISS). Data were collected from Asian, European and North American centers

from 1981 to 2002. The sample was comprised of 10,750 patients with symptomatic MM. Univariate and multivariate analyses identified statistically significant predictors of survival. The resulting model that emerged was a three-stage classification system that uses serum β_2-microglobulin and albumin (Greipp et al.). Table 2 summarizes the ISS.

Table 2. New International Staging System

STAGE	CRITERIA
I	Serum β_2-microglobulin <3.5mg/L Serum albumin >35g/L
II	Neither stage I nor III Serum β_2-microglobulin <3.5mg/L and serum albumin <35g/L or Serum β_2-microglobulin 3.5mg to 5.5mg/L irrespective of albumin
III	Serum β_2-microglobulin >5.5mg/L

Note. From "International staging system for multiple myeloma," by Greipp et al., *Journal of Clinical Oncology, 23,* p. 3412-3420. Copyright 2005 by the American Society of Clinical Oncology.

International Myeloma Working Group Response Criteria

A complete response (CR) is defined by negative immunofixation of serum and urine, disappearance of soft tissue plasmacytomas and ≤5% plasma cells in the bone marrow (Durie et al., 2006). In addition to these, a stringent complete response (sCR) requires a normal free light chain ratio, absence of clonal cells in the bone marrow by immunohistochemistry and immunofluorescence. A very good partial response (VGPR) is considered when serum and urine M-protein is detectable by immunofixation but not

by electrophoresis or ≥ 90% reduction in serum M-protein with urine M-protein level <100mg/24h. A partial response (PR) occurs when there is a ≥50% reduction of serum M-protein and reduction in 24h urinary M-protein by ≥90% or to < 200mg/24h. If both serum and urine M-protein are undetectable, a ≥50% in the difference between the involved and uninvolved free light chain levels is required. If serum and urine M-protein levels are unmeasurable and serum free light chain is also unmeasurable, a ≥50% reduction in plasma cells is required if baseline bone marrow plasma cells were ≥30%. If plasmacytomas present at baseline, a ≥50% reduction in size is required (Durie et al.).

Survival End Points

Progression free survival (PFS) is the interval from initiation of treatment to disease progression and/or death (Durie et al., 2006). Event free survival (EFS) is a variable term that may refer to progression, drug toxicity and death. Time to progression (TTP) refers to time from initiation of treatment to disease progression with deaths due to other causes removed. Disease free survival (DFS) is the time from start of complete response to time of relapse. Duration of response (DOR) refers to patients who have achieved at least a PR and is the interval from achievement of PR to disease progression with deaths due to causes other than progression removed (Durie et al.).

Chromosomal Abnormalities

Cytogenetic analysis provides valuable prognostic information and can assist clinicians in determining appropriate treatment strategies for patients with multiple myeloma. Because so few of the malignant cells are dividing at time of analysis, conventional karyotyping using cytogenetics does not reliably identify abnormalities in patients with myeloma (Fonseca et al., 2004). However, interphase fluorescence *insitu*

hybridization (FISH) detects chromosomal changes even in non-cycling cells. Consensus exists that patients with myeloma have one or more chromosomal abnormalities when measured by interphase FISH (Fonseca et al.). Deletion of chromosome 13, translocation 4;14 and p53 deletions have been associated with poor prognosis (Reece, 2005). More specifically, a recent study by Avet-Loiseau et al. (2007), found that translocation 4;14 and del(17p) were prognostically significant for event free and overall survival.

Treatment of Multiple Myeloma

There is no cure for MM to date although molecular complete responses have been attained in patients (MMRF, 2004). Relapses generally occur even after apparent initial disease eradication. This suggests that current clinical methods are unable to detect residual disease. Patients with symptomatic myeloma are typically initially treated with chemotherapy. For suitable candidates induction therapy may be followed by high dose chemotherapy and stem cell transplantation (Orlowski, 2006).

Proteasome inhibition.

The ubiquitin proteasome pathway (UPP), a proteolytic system present in the cytosol and nucleus of cells, regulates cyclin and cyclin-dependent kinase inhibitor proteins, thus regulating cell cycle progression (Hideshima, Richardson, & Anderson, 2004). The UPP is the primary pathway by which proteins in eukaryotic cells are degraded (Jung, Holle, & Dalton, 2004). Interfering with the degradation of important cell cycle regulatory proteins presents a targeted approach to inhibiting cellular proliferation.

Proteasomes are responsible for the degradation of greater than 80% of all cellular proteins, including those essential for tumor cell survival, proliferation, invasiveness ad

metastasis, angiogenesis and apoptosis. Inhibiting proteasomes prevents the degradation of various intracellular proteins. A consequence of this is alteration of downstream signaling cascades and disruption of cellular processes which ultimately leads to cell death (Jung et al., 2004).

Bortezomib (PS-341) is a novel proteasome inhibitor belonging to a class of peptide boronate proteasome inhibitors that specifically inhibit 26S proteasome activity (Hideshima et al., 2004). Inhibition of this proteasome has many downstream effects, including the inhibition of nuclear factor kappa B (NFκB) activation. NFκB is known to impart drug resistance and regulate adhesion molecule expression on MM cells and bone marrow stromal cells (BMSCs). It has also been found to influence constitutive and MM cell-induced cytokine transcription and secretion in BMSCs (Hideshima et al.).

Preclinical evaluation revealed that bortezomib impaired tumor cell growth, induced apoptosis, overcame resistance to conventional chemotherapeutic agents and radiotherapy and inhibited angiogenesis (Jung et al., 2004). With promising results from Phase I and Phase II trials, further studies evaluating bortezomib's efficacy are currently underway. Of note, the largest study to date, the SUMMIT trial, investigated bortezomib in 202 patients with MM (Jung et al.). In addition to the endpoint of survival, quality of life (QOL) was also evaluated in these patients. Patients reported experiencing a decline in disease related symptoms such as fatigue, pain and reported an overall improvement in QOL (Jung et al.).

Immunomodulatory drugs (IMiDs).

A derivative of glutamic acid, thalidomide inhibits TNF-α production and impairs angiogenesis (Hideshima et al., 2004). Thalidomide belongs to a pharmacological class

known as the immunomodulatory drugs (IMiDs). Although initially thought to function as an angiogenesis inhibitor, thalidomide was later found to be an immunomodulatory agent, prompting the development of a family of thalidomide-related IMiDs. These drugs have been found to induce G1 growth arrest and apoptosis in MM cells. Further, the IMiDs have the ability to inhibit NFκB activity in MM cells, with subsequent influence on cell survival, apoptosis and cytokine production (Hideshima et al.). Additional mechanisms by which the IMiDs exert anti-myeloma effects include the inhibition of adhesion of MM cells to BMSCs, inhibition of activity/secretion in MM cells/BMSCs of cytokines, impaired angiogenic activity and potential augmentative immunomodulatory effects (Hideshima et al.). The IMiDs, of which thalidomide and lenalidomide are the most frequently used, continue to be investigated for the treatment of MM.

Induction Therapy Prior to High Dose Therapy/Stem Cell Transplantation

High dose chemotherapy followed by autologous stem cell transplantation is considered standard therapy for patients with good performance status and no underlying organ dysfunction (Reece, 2005). If high dose therapy is planned, it is desirable to utilize induction therapy that will not jeopardize future attempts to mobilize stem cells. Autologous stem cell transplantation involves mobilization therapy with chemotherapy, generally cyclophosphamide, with or without growth factor such as granulocyte colony stimulating factor to stimulate production of hematopoietic progenitor cells (Imamura et al., 2005; To, Haylock, Simmons, & Juttner, 1997). Mobilization therapy stimulates the release of hematopoietic progenitor cells or 'stem cells' from bone marrow into peripheral blood. Apheresis involves removing mobilized blood which contains an elevated number of hematopoietic progenitor cells defined by the number of cells with a

stem cell phenotype (CD34+CD45lo). Following mobilization therapy and apheresis, the patient undergoes high dose chemotherapy with re-infusion of the stem cells thereafter. Once in the circulation, the stem cells home to the bone marrow and re-engraft (Cottler-Fox et al., 2003). In essence, the stem cells act as a 'rescue' to mitigate the harmful myelosuppressive effects of the high dose chemotherapy (To et al.).

The most commonly used first line regimens prior to proceeding to transplant are vincristine, adriamycin and dexamethasone (VAD), single agent dexamethasone or dexamethasone in combination with other agents (Hari, Pasquini, & Vesole, 2006). In general, patients receive several cycles of treatment over approximately 4 to 6 months prior to high dose therapy. Thalidomide has been investigated in combination with dexamethasone for induction therapy. A randomized study by Rajukumar, Blood, Vesole, Fonseca, & Greipp (2006) comparing single agent dexamethasone to thalidomide/dexamethasone (Thal/Dex) demonstrated significantly higher response rates with Thal/Dex (41% vs. 63%) with successful stem cell collection thereafter. Adverse events including deep vein thrombosis, rash, neuropathy and bradycardia were higher in the Thal/Dex arm (Rajkumar et al.). Lenalidomide containing regimens are being investigated though at this time, lenalidomide has only been approved for the treatment of relapsed/refractory myeloma (Cavo & Baccarani, 2006; Rajkumar et al., 2004). Other regimens being investigated as pre-transplant induction therapy include:

- melphalan, prednisone, thalidomide (MPT) (Palumbo et al., 2004)
- bortezomib, doxorubicin, dexamethasone (PAD) (Cavenagh et al., 2004)
- bortezomib, dexamethasone (VD) (Harousseau, et al., 2004)

- bortezomib, dexamethasone, thalidomide (VDT) (Wang, Weber, Delasalle, & Alexanian, 2004)
- bortezomib, dexamethasone, thalidomide, cisplatin, adriamycin, cyclophosphamide, etoposide (VDT-PACE) (Barlogie et al., 2005)
- bortezomib, melphalan, prednisone (VMP) Mateos et al., 2004)

High Dose Therapy and Autologous Stem Cell Transplantation

High dose therapy with stem cell transplantation is now the treatment of choice for patients with newly diagnosed MM with good performance status. To date, there have been five randomized clinical trials comparing conventional chemotherapy to high dose chemotherapy/stem cell transplant for first line therapy in newly diagnosed patients with MM. The responses have been variable. Two of the studies, the IFM90 (Attal et al., 1996) and MRC VII (Child et al., 2003) trials, demonstrated statistically significant improvements in both EFS and OS with high dose therapy/stem cell transplant when compared with standard chemotherapy. In the French MAG91 study, PFS was prolonged but there was no difference in OS (Fermand et al., 2005). The Spanish PETHEMA trial found no difference in either EFS or OS (Blade et al., 2005). The US Intergroup trial randomized 516 patients to either standard dose therapy or high dose therapy with no differences in PFS or overall survival (OS) at 7 years (median 76 months) follow-up (Barlogie et al., 2006). Table 3 summarizes the results of these studies.

Table 3. Comparison of standard dose therapy vs. high dose therapy/stem cell transplant

	N	age	Median EFS (months)	Median OS (months)
IFM90	200	≤65	18 vs. 28 P=0.01	44 vs. 57 P=0.03
MRC VII	401	≤66	19.6 vs. 31.6 P<0.001	42.3 vs. 54.1 P=0.04
MAG[a]	190	55-65	18.7 vs. 25.3 P=0.07	47.6 vs. 47.8 P=0.91
PETHEMA[b]	164	≤65	33 vs. 42 P=NS	61 vs. 66 P=NS
US Intergroup[c]	516	<70	21 vs. 25 P=0.05	53 vs. 57 P=NS

[a]22% salvage transplant at relapse in standard dose therapy

[b]only those responding to induction therapy were randomized into study

[c]cross-over rate of 52%

High dose therapy in patients >65y has been explored with similar event free and overall survival when compared to a matched group of younger patients (Qazilbash et al., 2007; Siegel et al., 1999). However, treatment-related mortality was higher in the older patients. Others have found no differences in treatment related mortality, event free survival and overall survival (O'Shea et al., 2006, Reece et al., 2003). Dose reductions in melphalan for patients >70 years are reportedly well tolerated while melphalan 200mg/m^2 has been associated with increased toxicity in these patients (Gertz, 2004; Reece, 2005).

Single versus Tandem Autologous Transplant

The efficacy of tandem transplantation has been studied by several researchers. In the French IFM94 trial, newly diagnosed patients <60years were treated with vincristine, adriamycin and dexamethasone followed by either a single autologous transplant or two autologous transplants (Attal et al., 2003). The conditioning regimen differed with the single transplant recipients receiving melphalan 140mg/m^2 and total body irradiation (8Gy) while the double transplant recipients received melphalan 140mg/m^2 with their first transplant and both melphalan 140mg/m^2 and TBI with their second. Both event free and overall survival were superior in the double transplant arm.

There are four additional trials that have studied tandem transplantation. Both the Bologna 96 study (Cavo, Cellini, & Zamagni, 2005) and the HOVON study (Sonneveld et al., 2005) identified improvements in event free survival though not in overall survival. However, overall survival was statistically significantly improved in the tandem group for patients who failed to achieve a CR/VGPR after the first transplant. The MAG95 study failed to demonstrate improvement in either event free or overall survival thus far (Fermand, 2005). Results from the German GMMG-HD2 study revealed statistically significant improvements in event free survival but not in overall survival (Goldschmidt, 2005).

In summary, patients who have not achieved at least 90% reduction in paraprotein level may derive benefit from a second transplant based on the results from the IFM94 and Bologna 96 trials (Hari et al., 2006). There is some evidence to suggest that patients with chromosome 13 deletion by FISH analysis have worse outcomes with tandem autotransplants and thus, this treatment may not be the best approach in these patients

(Blade, 2003; Hari et al.). Only the HOVON trial reported on QOL and found that QOL was superior with single transplant compared to tandem transplant (Hari et al.).

Timing of Transplant

While overall survival was comparable for early and late hematopoietic stem cell transplant for patients in the US Intergroup and MAG95 trials, quality of life was superior in patients receiving early transplantation (MAG95) (Hari et al., 2006). Fassas, Van Rhee, & Tricot (2003) identified superior event free and overall survival when tandem transplantation occurred within 12 months of diagnosis. More specifically, when tandem transplantation is planned, the second transplant should occur prior to relapse and within 6 to 12 months following the first transplant (Morris et al., 2004). Table 4 summarizes the results of single autologous stem cell transplantation versus double autologous stem cell transplantation for multiple myeloma.

Table 4. Comparison of single autologous transplant vs. tandem autologous transplant

	N	Median age	FU (Months)	EFS (%)	OS (%)
IFM94	399	60	76	25 vs. 30 P<0.05	48 vs. 58 P<0.05
Bologna 96	220	60	55	22 vs. 35 P<0.05	59 vs. 73[a]
HOVON 24MM	304	65	56	23 vs. 29 P<0.05	55 vs. 50 P= NS
GMMG HD2	261	65	NR	23 vs. 29 P<0.05	NS
MAG95	227	55	53	31 vs. 33 p=0.55	49 vs. 73[b] P=0.14

Note. FU = follow-up; NR = not reported

[a]Survival benefit for patients who failed to achieve complete response/very good partial response after first transplant

[b]Overall survival statistically significant only for non-CD34 selected tandem transplants in subgroup analysis

Allogeneic Transplant

Allogeneic stem cell transplantation has been found to be effective with lower relapse rates than autologous transplantation. This is thought to be due to graft-versus myeloma (GVM) effect as well as absence of tumor cell contamination in the graft itself (Reece, 2005). However, allogeneic transplant has been associated with increased

treatment-related mortality (TRM). Treatment-related mortality has been associated with stage of disease at diagnosis, number of previous prior therapies and development of grade 3-4 graft-versus-host disease (Hari et al., 2006). Additional TRM may be ascribed to increased infectious complications with allogeneic transplant (Blade, 2003).

Reduced intensity conditioning therapy (RICT) has resulted in reduced mortality while preserving the beneficial GVM effect (Reece, 2005). In the IFM99-03 trial, patients with a suitable allogeneic donor underwent autologous stem cell transplantation followed by reduced intensity conditioning therapy and allogeneic stem cell transplant (Moreau et al., 2003). The median progression free survival and overall survival rates were similar when compared to patients who underwent a second autologous stem cell transplant. The Spanish PETHEMA group studied allo-transplantation in patients <70 years who did not achieve a CR or near CR with one autologous stem cell transplant (Rosinol et al., 2005). The patients were treated with a second autograft or a reduced-intensity allogeneic stem cell transplant. The patients who underwent allotransplant achieved a higher CR rate but encountered more treatment-related mortality with similar overall survival rates between the two groups (Rosinol et al.).

A recent study by Martino et al. (2006) enrolled 15 patients with newly diagnosed MM. The participants underwent high dose therapy with melphalan (200mg/m^2) and autologous peripheral blood stem cell transplantation followed 3 to 4 months later by RIC with fludarabine plus cyclophosphamide and then allogeneic stem cell transplantation. The authors reported high rate of CR (73%) and low toxicity with median follow-up of 44 months (Martino et al.). These results were confirmed by a recent Italian study comparing tandem autologous stem cell transplant to autotransplant followed by HLA-

matched sibling (Bruno et al., 2007). The group that underwent allogeneic transplant after autograft had improved EFS and OS (80 vs. 54 months [p=0.01] and 35 vs. 29 months [p=0.02] respectively). On multivariate analysis these results remained significant. Treatment-related mortality did not differ between the two groups. However, while Garban et al. (2006) reported reduced TRM with RICT allogeneic stem cell transplant after autotransplant, overall survival was not improved in patients with newly diagnosed multiple myeloma.

Post-transplant Maintenance

A National Cancer Institute of Canada (NCIC) trial comparing thalidomide maintenance at a dose of 200mg daily plus alternate day prednisone to observation alone following high-dose therapy and stem cell transplant is ongoing. The IFM99-02 randomized patients to receive pamidronate, pamidronate plus thalidomide 100mg daily or observation following autologous stem cell transplantation. Interim results have been reported with significant improvement in progression free survival with pamidronate and pamidronate plus thalidomide compared to observation (Reece, 2005). An Italian study assessing safety and feasibility of thalidomide maintenance following autologous stem cell transplantation recently reported that patients (n=17) encountered high toxicity and low tolerance of thalidomide (Martino et al., 2007). Lenalidomide versus observation is being studied in the CALGB 100104 trial. Other post autologous stem cell transplantation treatments that are being studied include some of the newer agents being used to treat MM. For example, the Total Therapy III regimen includes VDT-PACE [bortezomib, dexamethasone, thalidomide, cisplatin, adriamycin, cyclophosphamide, etoposide] and

VTD [bortezomib, thalidomide, dexamethasone] after tandem autologous stem cell transplantation.

Induction Therapy for Non-transplant Candidates

Almost half of patients with MM are not eligible for high dose therapy and stem cell transplant because of age or organ dysfunction. For patients who are not eligible to receive high dose chemotherapy and stem cell transplant, melphalan or cyclophosphamide with or without prednisone is standard therapy. Other combinations such as melphalan, prednisone and thalidomide are being investigated for initial therapy when transplant is not an option. Palumbo et al. (2004) investigated melphalan, prednisone and thalidomide (MPT) compared to melphalan and prednisone (MP) in newly diagnosed patients. The MPT combination yielded significant improvements in CR rates and EFS however, also induced higher rates of adverse events. A phase I/II trial of melphalan, prednisone and bortezomib (MPV) in elderly patients demonstrated significant improvements in response rates compared to historical controls (National Comprehensive Cancer Network [NCCN]c, 2007). Studies comparing MPV to MP are ongoing. The results of a phase II trial of thalidomide, dexamethasone and pegylated liposomal doxorubicin (ThaDD) were recently reported (Offidani et al., 2006). The participants in the study had newly diagnosed MM and were older than 65 years. The regimen was found to be effective with manageable toxicity (Offidani et al.).

Treatment of Relapsed/Refractory Multiple Myeloma

The goals of treatment for relapsed myeloma are to control disease, improve symptoms/QOL and prolong survival (Smith et al., 2006). Melphalan and prednisone (MP) is a common regimen for relapsed myeloma. Thalidomide has also been useful in

treating relapsed MM, either as a single agent or in combination with dexamethasone. As a single agent, thalidomide has been found to induce responses in 30% of relapsed or refractory patients with MM (Smith et al.). Higher response rates, up to 60%, have been reported when thalidomide is combined with dexamethasone and dexamethasone plus cyclophosphamide (Smith et al.). Bortezomib has also led to responses in approximately 30% of relapsed patients with further responses reported with the addition of dexamethasone to bortezomib. Studies examining the efficacy of thalidomide, thalidomide-analogues and bortezomib in various combinations with other medications are ongoing (Smith et al.).

In their article on guidelines for the diagnosis and management of patients with multiple myeloma, Smith et al. (2006) describe an algorithm for the treatment of relapsed myeloma. For patients initially treated with melphalan/prednisone (MP) or cyclophosphamide who have attained remission >6 months, it is considered reasonable to re-treat with MP or cyclophosphamide. For those relapsing within 6 months, thalidomide is suggested for 8-10 weeks' duration. If no response, the addition of dexamethasone with/without cyclophosphamide is recommended. If no response or second relapse, third-line therapy might include bortezomib, cyclophosphamide, or dexamethasone either as single agents or in various combinations (Smith et al.).

For relapsing patients initially treated with vincristine, adriamycin and dexamethasone (VAD) or a similar regimen followed by high dose therapy and stem cell transplant who are 12-18 months post transplant, reinduction therapy followed by a second stem cell transplant is recommended (Smith et al., 2006). For those relapsing within 12 months, a trial of thalidomide for 8-10 weeks is suggested with the addition of

dexamethasone with/without cyclophosphamide if no response is attained. Second relapses should be treated with bortezomib, cyclophosphamide, or dexamethasone either as single agents or in various combinations (Smith et al.).

Treatment for relapsed/refractory myeloma is contingent upon numerous patient-specific factors including length of previous CR, number/type of previous treatment(s), age and performance status of patient. Regardless of the treatment approach, good supportive care with attention to pain/symptom management and psychosocial distress is imperative (Smith et al., 2006).

Fatigue and Multiple Myeloma

As the malignant clone proliferates skeletal destruction, bone marrow failure, increased plasma volume/blood hyperviscosity, suppression of normal immunoglobulin production and renal failure occur (IMF, 2004). As a result, individuals with MM encounter profound symptom distress (Durie et al., 2003; Stead et al., 1999). Fatigue represents one of the most commonly reported symptoms in individuals with MM. Individuals with MM have fatigue for several reasons. The most recognized theory is that fatigue in individuals with MM is a consequence of anemia.

Anemia as an Explanation for Fatigue in Patients with Multiple Myeloma

Anemia in MM patients is likely a function of both the disease process itself and treatment. A potential mechanism underlying fatigue in MM patients may be that, as disease progresses, there is reduced production of erythropoietin due to renal function impairment, resulting in decreased hemoglobin and fatigue. This position is supported by the fact that anemia is common at diagnosis. In their analysis of 1027 individuals with MM, Kyle et al. (2003) found that 73% presented with anemia at initial diagnosis. Other

authors have estimated the prevalence of anemia in MM to be consistent with this figure, at approximately 62-100% (Knight et al. 2004). In addition, anemia in MM patients is exacerbated by myelosuppressive therapy. Typically, the anemia associated with MM is normochromic and normocytic (San Miguel et al., 2002).

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Reasons for anemia in individuals with MM may include:

- shortened erythrocyte survival and subsequent failure of the bone marrow to compensate by increasing red blood cell (RBC) production.
- decreased RBCs due to impaired availability of stored iron, inadequate erythropoietin response, overproduction of cytokines that inhibit erythropoiesis (IL-6, IL-1, TNF), decreased reutilization of iron stores from reticuloendothelial cells, interference with erythropoietin by the kidneys, defective RBC production by bone marrow (due to infiltration by MM cells or myelosuppressive treatment) (Lokhorst, 2002)
- low serum erythropoietin (Ludwig, Pohl, & Osterborg, 2004)

Palumbo et al. (2002) discussed the relationship between fatigue, QOL, hemoglobin and selected patient characteristics. Their study, which included 1071 patients with MM, recruited its sample from 24 Italian oncology centers between November 2001 and March 2002. The cohort comprised 22% newly diagnosed MM patients while the remainder was made up of patients in remission (57%), those who

relapsed (15%) and those who had no response (6%). The majority of participants had Stage III disease (58%), while 27% of patients had Stage II disease and 15% had Stage I disease. The bulk of the sample had undergone at least one type of treatment (78%), while 76% were undergoing therapy at time of study enrollment.

The mean hemoglobin was 11.9 ± 1.9g/dL. The authors reported differences in mean hemoglobin according to gender (m 12.2g/dL, f 11.6g/dL), age (<50y: 12.4g/dL, 51-60y: 12.2g/dL, 61-70y: 11.8g/dL, >70y: 11.6g/dL), response rate (no response/relapse: 11g/dL, remission: 12.4g/dL). The latter could represent support for a common underlying mechanism inducing both anemia and the pathogenesis of MM. Further differences in mean hemoglobin were found in patients with different stage of disease (Stage I: 12.5g/dL, Stage II: 11.9g/dL, Stage III: 11.7g/dL). Though differences in hemoglobin were found between patients receiving chemotherapy and those not, the effect of concurrent chemotherapy was not significant after adjusting for hemoglobin and additional covariates.

Another Explanation for Fatigue in Multiple Myeloma

There is growing evidence that other factors related to the inflammatory process may contribute to fatigue in patients with MM. Mazhar, Gillmore, & Waxman (2005) discuss the role of inflammation in the pathogenesis of malignancy. Overexpression or aberrant expression of proinflammatory cytokines have been identified as an essential component of tumor progression and proliferation. It is hypothesized that these same cytokines also contribute to the development of cancer related symptoms including lean tissue loss, poor performance status, fatigue and anemia (Brown et al., 2005; Kurzrock, 2001).

When these proinflammatory cytokines occur in the bone marrow microenvironment, they contribute to the pathogenesis of MM (Harousseau & Moreau, 2002). In particular, the production and secretion of certain cytokines is thought to confer proliferative and survival benefits to MM cells. Further, these cytokines are also capable of conferring drug resistance and anti-apoptotic properties.

Nuclear factor kappa b (NFκB) has been found to regulate adaptive and innate immune responses (Lee et al., 2004). NFκB controls the activity of several cytokines, chemokines, cell surface adhesion molecules and certain receptors (Lee et al.). Further, NFκB activates expression of genes coding for enzymes that participate in the inflammatory process. The subsequent result is inducible expression of COX-2 and production of prostaglandins. Lee et al. note that prostaglandins are known to induce symptoms associated with sickness such as fatigue, lethargy, and fever and suggest that NFκB could represent a possible link between the expression of cytokines and the production of cancer related symptoms.

Interleukin-6.

Interleukin-6 (IL-6) influences both growth and survival of MM cells (Trikha, Corringham, Klein & Rossi, 2003). IL-6 is overproduced by bone marrow stromal cells (BMSCs) and elevations have been found in active and advanced disease (Hideshima, Bergsagel, Kuehl, & Anderson, 2004; Van Zaanen et al, 1998). Specifically, IL-6 has been found to influence JAK (anti-apoptosis), RAF (proliferation) and PI3K (migration/anti-apoptosis/cell cycle) pathways. Inhibitors of IL-6 include corticosteroids, nonsteroidal anti-inflammatory drugs, estrogens, and other cytokines. A common

component of many MM treatment regimens, dexamethasone, has been found to inhibit IL-6 and IL-6R gene expression (Trikha et al.).

Increased IL-6 production has been found in patients with Alzheimer's disease, autoimmunity (in particular, rheumatoid arthritis), myocardial infarction, Paget's disease, osteoporosis, solid tumors (renal cell carcinoma), prostate and bladder cancer, neurological cancer, and B cell malignancies (Castleman's disease, some lymphomas, chronic lymphocytic leukemia, and MM) (Trikha et al., 2003). Additionally, serum IL-6 has been found to be increased in patients with chronic fatigue syndrome (Dimeo et al., 2004). The relationship between IL-6 and anemia has yet to be identified though theories are emerging.

Hepcidin, a peptide produced by hepatocytes and induced by IL-6, is an iron regulatory hormone responsible for the inflammation-induced iron dysutilization implicated in the anemia related to acute and chronic infection and chronic renal disease and is hypothesized to play a role in anemia related to malignancy (Andrews, 2004; Maccio et al., 2005; Riveria et al., 2005). Nemeth et al. (2004) found that the infusion of IL-6 in humans led to increased hepcidin secretion, decreased serum iron and decreased transferrin saturation. Importantly, the hepcidin-induced altered iron utilization is not observed in IL-6 knockout mice (Nemeth et al.). IL-6 induces the transcription and translation of ferritin and induces hepcidin, which ultimately leads to increased storage of iron in the reticuloendothelial system (RES) and hypoferremia. Hypoferremia then results in a blunted erythropoietin response and subsequent anemia (Nemeth et al.). Thus, elevated IL-6 may contribute to anemia in patients with MM.

Evidence for the impact of IL-6 on the development of cancer-related symptoms is supported by the administration of anti-IL-6 therapy in patients with MM. In an early trial of patients with advanced MM receiving anti-IL-6 monoclonal antibody therapy, Bataille et al. (1995) reported that patients experienced subjective improvement in both pain and fatigue along with reductions in C-reactive protein levels. Further, patients who had previously been experiencing fever and hypercalcemia had resolution of these symptoms. When Rossi et al. (2005) infused patients with MM with an anti-IL-6 monoclonal antibody (MAb), they found that the MAb was able to block in vivo proliferation of MM cells and reduce IL-6 related symptoms such as fever and cachexia. Further, patients treated with the MAb required fewer transfusions of red cells as compared with the control group ($p<0.01$). While several researchers have reported on the ability of anti-IL-6 MAbs to reduce symptoms such as fever and cachexia this has been tempered with modest clinical response as far as control of MM though for the most part these agents have been trialed in patients with advanced or refractory MM (Trikha et al., 2003; van Zaanen et al., 1998).

C-reactive protein (CRP).

C-reactive protein (CRP) is an acute phase protein produced by hepatocytes. The production of CRP is regulated by IL-6 in vitro and in vivo (Trikha et al., 2003). Rossi et al. (2005) found that CRP production was blocked in patients receiving an anti-IL-6 monoclonal antibody. This is confirmed by the lack of production of CRP in IL-6 knockout mice (Rossi et al.).

Fatigue and Quality of Life (QOL) in Multiple Myeloma

Because MM represents, as yet, an incurable malignancy, goals of therapy continue to focus on the alleviation of symptoms, preservation of wellbeing and prevention of relapse and disease progression (MMRF, 2004). It has been well documented that MM causes pronounced symptom distress from bone pain, fractures, recurrent infections and fatigue (Durie et al., 2004; Stead et al., 1999), which influence quality of life. Quality of life is a global appraisal of the individual's subjective experience on a physical, social, and emotional level. In an unblinded trial comparing melphalan/prednisone to melphalan/prednisone and interferon, Wisloff & Hjorth (1997) concluded that QOL may be an independent prognostic factors for individuals with MM.

Summary

Fatigue is one of the most commonly reported symptoms in cancer. For individuals with MM, fatigue is almost certain to occur at some point along the illness trajectory. In attempts at unraveling the complexities of fatigue, some relationships have been established, while others remain unstudied or unsubstantiated.

Anemia and fatigue are generally correlated; however, research has demonstrated that the two are not consistently associated with one another. This suggests that alternative or additional processes influence fatigue. For example, anemia does not always increase as disease progresses or, may increase at times not as a reflection of disease progression but rather as a response to myeloablative therapy. Similarly, fatigue does not always increase as disease progresses and alternatively, may even be severe in the absence of disease progression or anemia. The alternate/additional processes of interest in this study are related to inflammation and tumor burden.

The diversity of potential causes of fatigue in cancer patients may be a consequence of unique underlying pathologic mechanisms of fatigue in different types of cancers (Gutstein, 2001). If this is the case, tailoring therapies to specific pathologies may result in more effective treatment. Gutstein suggests that further evaluation of the pathology of fatigue may lead to greater understanding of how patients respond to therapy. He questions whether there are correlations between the clinical and biochemical status of the patient and response to specific therapies. Characterizing biologic and clinical correlates of fatigue will lead to a greater overall understanding of fatigue. This study is part of a program of research designed to identify disease and treatment factors that lead to fatigue. The ultimate intention behind this endeavor is to improve patient care with innovative symptom management interventions.

Chapter 3: Methods

Design

The study employed a prospective, descriptive exploratory design.

Sample

A consecutive sampling approach was used to accrue 56 individuals from the MM clinics at the Tom Baker Cancer Center (TBCC). As there are 2 independent variables (hemoglobin and C-reactive protein), a minimum of 20 patients was required. This sample size prediction was based upon the minimum requirement of 10 patients per independent variable for regression (Cohen, 1977).

Inclusion criteria:

- diagnosis of MM, attendance at the TBCC MM clinics;
- age ≥18 years old and consent to participate in the study.

Exclusion criterion:

- patients with a diagnosis of a plasma cell dyscrasia other than MM (for example, monoclonal gammopathy of unknown significance (MGUS);

Data Collection

Following ethics approval, study candidates were approached in MM clinics and provided with a written explanation of the study and its purpose. Once consent (Appendix A) was obtained, individuals were asked to complete the FACT-F and the EORTC-QLQC30/MY24. Demographic and clinical information including age, gender, disease stage, hemoglobin and CRP were obtained from each individual's chart.

Data collection occurred at one time point: when the patient visited TBCC for an outpatient hematology visit. This approach did not require the collection of any additional

blood or additional clinic visits since individuals are routinely assessed by physicians/nurses and have blood drawn at the TBCC prior to their clinic visit. The tests results analyzed here were obtained as part of the routine clinical screening for MM patients.

Instrumentation (Appendix B)

The European Organization for Research and Treatment of Cancer QLQC30

In 1986, the EORTC developed a comprehensive, modular method of assessing QOL in patients with cancer involved in clinical trials (Aaronson et al., 1993). The instrument was developed cross-culturally and cross-nationally (Kaasa et al., 1995). The field testing involved participation by researchers in 13 countries. The EORTC-QLQC30 has been translated and validated in 63 languages and used in more than 3000 studies throughout the world (EORTC, 2005).

The EORTC-QLQC30 is a 30 item questionnaire. It is comprised of subscales that assess physical function, role function, emotional function, social function and cognitive function. Also evaluated, are global QOL and symptoms (fatigue, pain, emesis, distress induced by financial concerns, dyspnea, sleep disturbance, appetite, diarrhea, constipation). Patients are asked to reflect on the past week when completing the questionnaire. Questions are configured as yes/no or by using four-answer categories (ranging from 1, not at all, to 4, very much). The questions on global QOL and general health are measured by a visual analog scale (1 to 7). Though initially developed to evaluate quality of patients participating in clinical trials, the EORTC-QLQC30 has also been utilized and evaluated in patients with advanced cancer (Kaasa et al., 1995). The EORTC-QLQC30 has been reportedly well received by patients, takes approximately 11

to 12 minutes to complete and typically, can be completed by patients independently (Aaronson et al., 1993).

Validity of the EORTC- QLQC30.

Interscale correlations were found to be statistically significant ($p<.01$) though were only of a moderate size. The authors report that this reflects that although subscales are related, each assesses distinct aspects of QOL (Aaronson et al., 1993). Construct validity of the EORTC-QLQC30 was evaluated by Kaasa et al. (1995) by assessing the magnitude of correlation among the subscales. The authors considered a correlation greater than 0.70 as unfavorable as it would not respond to the distinctness of the constructs being assessed (Kaasa et al.). Criterion validity was verified by high correlation with the General Health Questionnaire, 20 item version.

Reliability of the EORTC- QLQC30.

Hjermstad, Fossa, Bjordal and Kaasa (1995) evaluated the test/re-test reliability of the EORTC-QLQC30. The Pearson's correlation coefficient ranged from .63 to .91. The correlation coefficient for global QOL was .85 and the internal consistency evaluation generated Cronbach's α coefficients of 0.59 to 0.85. Kaasa et al. (1995) reported similar reliability coefficients. In their study, the range for the Cronbach's α was 0.62 to 0.89 before treatment and 0.67 to 0.92 after treatment. The lowest reliability occurred in the role and cognitive functioning scales. These results were repeated by Hjermstad, Fayers, Bjordal and Kaasa (1998), who found internal consistency evaluation to yield Cronbach's α of 0.59 to 0.85. Wisloff et al. (1996) found the EORTC-QLQC30 to be a valid and reliable instrument when used to assess QOL in patients with MM.

EORTC-MY24

A myeloma-specific QOL questionnaire was developed by Stead et al. (1999) in collaboration with the EORTC Quality of Life Study Group. This 24-question module is intended to be used as an adjunct to the EORTC-QLQC30, which is a general quality of life oncology questionnaire. While the myeloma module development process has been approved by the EORTC Quality of Life Study group, the module is still undergoing international field testing. At this time, there is no psychometric information available. Permission to utilize the module was granted by its authors.

The Functional Assessment of Cancer Therapy Fatigue (FACT-F)

The FACT-F is comprised of the 28 items of the FACT-general (FACT-G) as well as 13 items to assess fatigue. The FACT-G is a collection of questions that assess health related quality of life (Yellen, Cella, Webster, Blendowski & Kaplan, 1997). The FACT-F was developed in 1994. Validity of the FACT-F was evaluated by comparing results with the Piper Fatigue Scale, the Fatigue and Vigor subscales of the Profile of Mood States (POMS), a short form of the Marlowe-Crowne Social Desirability Scale and Eastern Cooperative Group (ECOG) performance status. The FACT-F was found to be positively correlated with other measures of fatigue. The 41 item FACT-F was found to be stable, with a test-retest correlation coefficient of 0.87. Internal consistency was also high with a Cronbach's α of 0.95. On its own, the authors report the 13-item fatigue subscale had a Cronbach's α of 0.93-0.95 (Ahlberg , Ekman, Gaston-Johansson, & Mock, 2003).

The time to complete the FACT-F is approximately 10 minutes. The FACT-F has been developed at a sixth grade reading level (Yellen et al., 1997). The fatigue subscale

has been reported to be brief, simple and straightforward to complete and may be used on its own. A potential limitation of this scale is that it has been designed for patients undergoing treatment. However, most of the myeloma patients accrued in this study were undergoing treatment of some kind at data collection. Permission to use this tool, along with scoring information, was provided by its authors.

Data Analysis

Statistical information was computed utilizing SPSS version 14.0 for Windows. Descriptive statistics were computed for all variables. Pearson's r was used to examine correlations amongst variables. Multiple linear regression was used to explore relationships between inflammation, anemia, fatigue, energy and quality of life. The correlation and regression results were confirmed using GraphPad Prism Version 4.00 for Windows, GraphPad Software, San Diego California USA, www.graphpad.com.

Ethical Considerations

All procedures in this study were conducted in accordance with the ethical standards outlined by the University of Alberta (2004) and the Alberta Cancer Board (2004). The research ethics boards (REB) at both the University of Alberta and the University of Calgary Conjoint Health Research Ethics Board (CHREB) were contacted and approval was obtained for the study.

Upon initial contact, potential study participants were informed of the study's purpose and of the study requirements, that participation was voluntary, and that withdrawal at any point during the study could occur without consequence. Further, individuals were provided with an information sheet explaining the study and outlining his/her rights as a participant in the study. Permission was also requested to contact

participants following completion of the study if subsequent research by the Alberta Myeloma Nursing Research Group required additional information. Any further studies would be submitted for ethical clearance from the appropriate ethics review committees.

Potential participants were advised that no harm or perceived risks related to the study were anticipated. Individuals were reminded that they did not have to complete any item on the FACT-F or EORTC-QLQC30/MY24 that made them feel upset or uncomfortable. Participants were informed that all data collected would be kept confidential. Following the initial data gathering process, all participants were assigned a study number which was used throughout the duration of the study to preserve anonymity. Participants' names and related identifying information were only included on the consent form, which is stored separate from the data in a secure cabinet.

Chapter 4: Results

Participants

Fifty seven patients were approached and asked to participate in the study. Of these, only one patient declined participation citing disinterest as the reason for declining. The resultant sample was comprised of 56 patients who attended outpatient hematology clinics between May 2006 and January 31, 2007. Of these, 53.6% (30) were men and 46.4% (26) were women. The mean age was 61.96 years (SD 10.027) with a range of 41-84. The majority (50%) of participants had Stage III disease while 21.4% had Stage II disease and 23.2% had Stage I disease. Information on Stage was missing in 5.4% of cases. The most common diagnoses were defined as having IgG Kappa (41.4%), IgA Kappa (14.3%) and IgG Lambda (12.5%) myeloma.

Time From Diagnosis

The mean number of months from diagnosis was 22.19 (SD 19.74). In three cases, it was not possible to determine the time from diagnosis as only the year of diagnosis was reported in the patient chart. The year of diagnosis for these cases was 1979, 1999 and 2002 respectively. The minimum time from diagnosis to time of participation in the study was one month and the maximum time was 77 months. This is reflective of the current overall median survival of approximately 3-5 years in individuals with multiple myeloma.

Cytogenetics

Cytogenetic information was not available in 26.8% of cases due to low or absent bone marrow plasma cell involvement. For those with cytogenetics reported, 37.5% were found to have none of the abnormalities being tested, 30.4% had del(13), 12.5% had translocation (4;14), and 3.6% had del(17p).

Past Medical History

The most common co-morbid condition in the sample was hypertension (33.9%) followed by Type II diabetes mellitus (16.1%). Several patients had a history of gastrointestinal conditions including diverticulosis (8.9%), diverticulitis (3.6%), GI bleed (10.7%), and cholecystectomy (5.4%). Ten patients (17.9%) of the sample had a history of appendectomy. Seven patients (12.5%) had a history of an additional cancer: prostate cancer (3), breast cancer (2), lymphoma (1) and cervical (1). Table 5 summarizes the demographic and clinical information on study participants.

Table 5. Demographics

	Mean	Min	Max
Age	61.96	41	84
Months since diagnosis	22.19	1	77
	Male	Female	
Gender	53.6% (30)	46.4% (26)	
Cytogenetics			
Available	73.2% (41)		
		Del 13	41.5% (17)
		Del 17p	4.9% (2)
		t(4;14)	17.1% (7)
		Not detected	51.2% (21)
Not available	26.8% (15)		

Table 5. Demographics

Classification		
	IgG Kappa	41.4% (23)
	IgA Kappa	16.1% (9)
	IgG Lambda	12.5% (7)
	Other	30% (17)
Stage		
	I	23.2% (13)
	II	21.4% (12)
	III	50% (20)
	Not available	5.4% (3)

Variables

Hemoglobin

Hemoglobin data were available for 55 participants. The minimum hemoglobin was 81g/L while the maximum was 151g/L with a mean of 117.73 (SD 16.93). By National Cancer Institute criteria 90% of the men in the sample were anemic and 72% of the women were anemic (using 140g/dL and 120g/dL respectively) (NCCNb, 2007).

C-reactive protein (CRP)

C-reactive protein data were available for 49 participants. The minimum CRP level was 0.2 mg/L and the maximum was 83.0mg/L with a mean of 11.48 (SD 16.19).

EORTC-QLQC30

The EORTC-QLQC30 questionnaires were scored to provide a total symptom score with the higher number representing more symptoms. There were 56 questionnaires available for scoring. The minimum total symptom score was 28, the maximum was 92 and the mean was 57.36 (SD 14.77).

EORTC-QLQC30 – Fatigue Subscale

The Fatigue Subscale has three items (10, 12, and 18) that assess fatigue on a scale of 1 to 4 where 4 represents more fatigue. The score for the subscale requires conversion to a linear representation via the formula Raw Score = (Q10+Q12+Q18)/3 to give a raw score. The Fatigue score is then computed via the formula: [(raw score)-1]/3 x 100. A high aggregate score represents more, or worse, fatigue while a low score represents less fatigue. In this study only 5.4% (3) of individuals reported no fatigue at all while 16.1% (9) reported the worst possible fatigue with an adjusted score of 100. The mean adjusted EORTC-QLQC30 fatigue score for the aggregate panel of questions was 56.75 (SD 29.66) with a minimum score of 0 and maximum score of 100.00.

Overall QOL

Item thirty on the EORTC-QLQC30 questionnaire asks the individual to rate his/her overall QOL on a scale of 1 to 7, with 7 being 'excellent' and 1 being 'very poor'. Five patients (8.9%) reported 'very poor' overall QOL and four patients (7.1%) reported 'excellent' overall QOL. The majority of individuals (53.6% [30]) reported a QOL score of 4 or 5.

Energy (FACT-F)

The FACT-F questionnaires were scored according to the scoring guidelines. The higher the total score, the better the individual's energy level or, in other words, the individual reported less fatigue. The highest possible score is 52.00 which would reflect no reported fatigue. One patient (1.9%) had a score of 52.00 while 2 patients (3.8%) had a score of 7.00.The mean score was 29.64 (SD 12.08) with a range of 7.00 to 52.00. The EORTC-QLQC30 fatigue score and the FACT-F fatigue score were highly correlated with one another ($r=0.88$, $p<0.01$).

A summary of the number of participants for whom data were available on each study variable, along with minimum, maximum, and mean scores, is shown in Table 4.

Table 6. Study Variables

	N	Mean	Min	Max
Hb (120-160g/L)	55	117.73	81	151
CRP (0-8.0mg/L)	49	11.48	0.2	83
Overall QOL (1-7)	56	4.11	1	7
Fatigue EORTC-QLQC30 (0-100)	56	56.75	0	100
Energy (FACT-F) (0-52)	53	29.64	7	52

Note. CRP=C reactive protein; Hb=hemoglobin; QOL=quality of life

Correlations

Hemoglobin and Fatigue

The relationship between hemoglobin and patient reported fatigue was examined using both measures of patient reported fatigue (Fatigue EORTC-QLQC30 and FACT-F). There was a negative relationship between Hb and fatigue using the EORTC-QLQC30 fatigue subscale with a correlation coefficient of -0.352 (P=0.008). In particular, as hemoglobin increased, fatigue scores decreased and conversely, as hemoglobin decreased, fatigue increased.

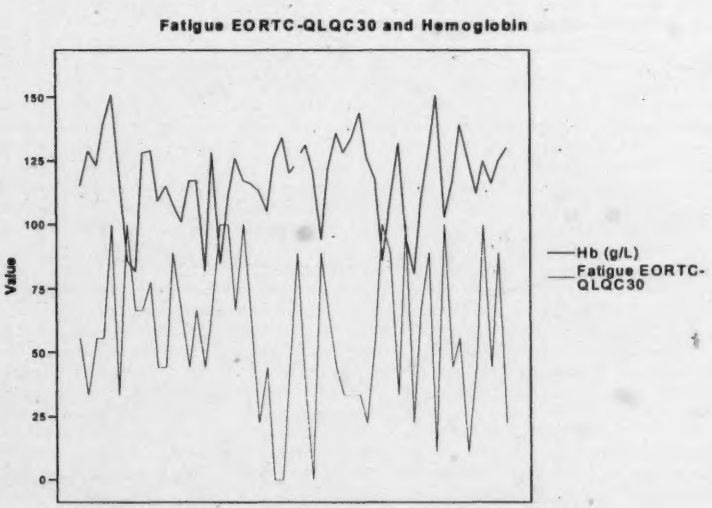

Figure 1. Fatigue EORTC-QLQC30 and Hemoglobin

Using the FACT-F, this relationship was confirmed, with a correlation coefficient of 0.432 (P=0.001). As hemoglobin increased, energy level (or lack of fatigue) also increased.

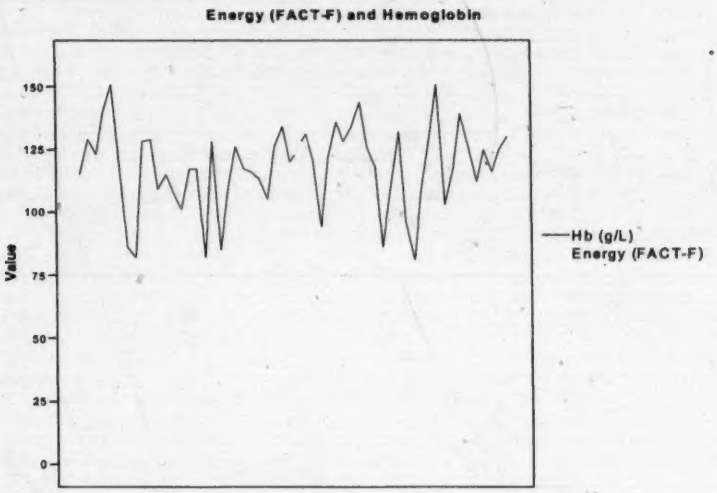

Figure 2. Energy (FACT-F) and Hemoglobin

C-reactive Protein and Fatigue

The relationship between CRP and patient reported fatigue was examined using both measures of patient reported fatigue. There was a positive relationship between CRP and fatigue using the EORTC-QLQC30 subscale with a correlation coefficient of 0.503 ($P<0.00001$). As CRP increased, fatigue also increased and conversely, as CRP decreased, fatigue decreased.

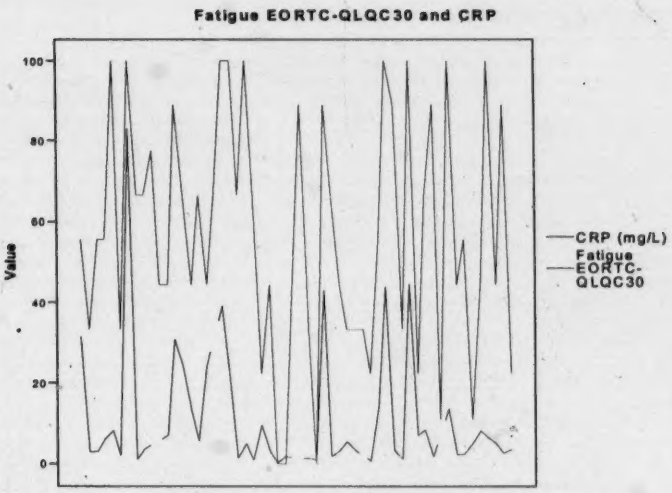

Figure 3. Fatigue EORTC-QLQC30 and CRP

This relationship was confirmed when the FACT-F was used to measure patient reported fatigue with a correlation coefficient of -0.459 (P=0.001). As CRP increased, energy level decreased.

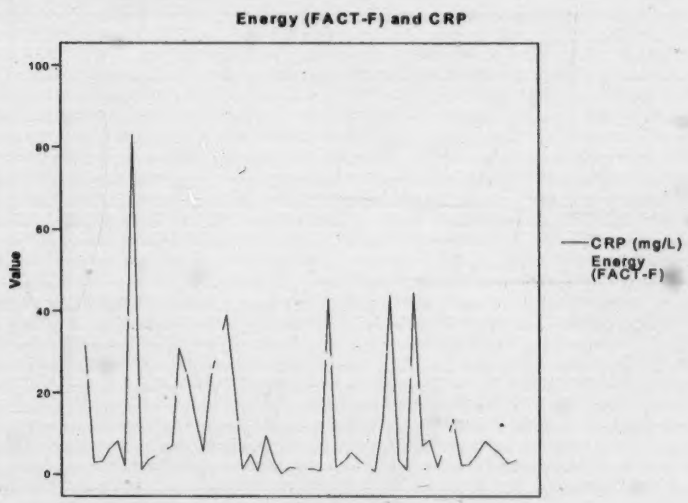

Figure 4. Energy (FACT-F) and CRP

Hemoglobin and Quality of Life

There was a positive relationship between hemoglobin and overall QOL with r=0.406 (*P*=0.002). Quality of life increased as hemoglobin increased and decreased as hemoglobin decreased.

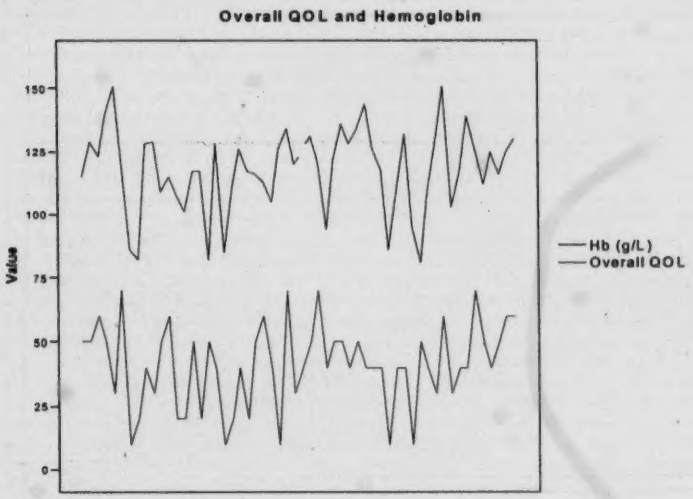

Figure 5. Overall QOL and Hemoglobin

C-reactive Protein and Quality of Life

There was a negative relationship between CRP and overall QOL as well with a correlation coefficient of -0.524 (*P*<0.00001). As CRP increased, QOL decreased and as CRP decreased, QOL increased.

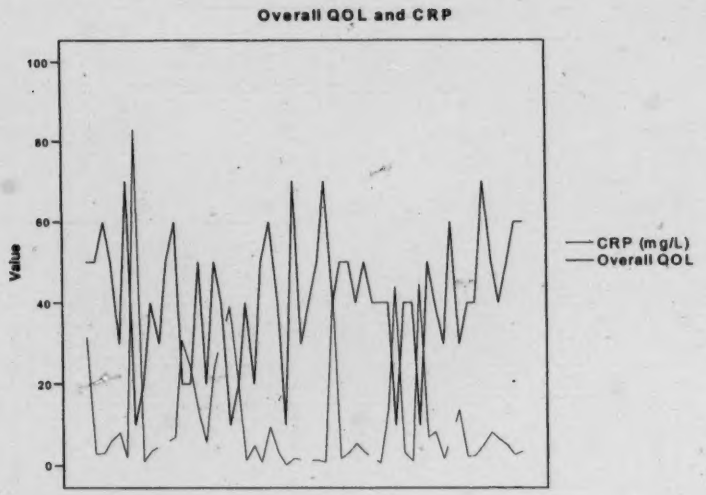

Figure 6. Overall QOL and CRP

Time From Diagnosis

Time from diagnosis was not correlated significantly with Fatigue EORTC-QLQC30 (P=0.215), Energy (FACT-F) (P=0.285) or overall QOL (P=0.940).

Stage of Disease

There were no significant relationships between stage of disease and hemoglobin (P=0.504), CRP (P=0.234), Fatigue EORTC-QLQC30 (P=0.141), Energy (FACT-F) (P=0.166) or overall QOL (P=0.787).

Table 7 summarizes the correlations found among the clinical variables (CRP, Hb), patient reported fatigue and patient reported quality of life.

Table 7. Correlations among study variables

	CRP	Energy (FACT-F)	Fatigue EORTC-QLQC30	Hb	Overall QOL
CRP					
Pearson	1	-0.459	0.503	-0.622	-0.524
Sig (2 tailed)		*P*=0.001	*P*<0.00001	*P*<0.00001	*P*<0.00001
N	49	47	49	49	49
Energy (FACT-F)					
Pearson	-0.459	1	-0.883	0.432	0.602
Sig (2 tailed)	*P*=0.001		*P*<0.00001	*P*=0.001	*P*<0.00001
N	47	47	53	52	53
Fatigue EORTC-QLQC30					
Pearson	0.503	-0.883	1	-0.352	-0.627
Sig (2 tailed)	*P*<0.00001	*P*<0.00001		*P*=0.008	*P*<0.00001
N	49	53	56	55	56

Table 7. Correlations among study variables

	CRP	Energy (FACT-F)	Fatigue EORTC-QLQC30	Hb	Overall QOL
Hb					
Pearson	-0.622	0.432	-0.352	1	0.406
Sig (2 tailed)	*P*<0.00001	*P*<0.001	*P*<0.008		*P*=0.002
N	49	52	55	55	55
Overall QOL					
Pearson	-0.524	0.602	0.627	0.406	1
Sig (2 tailed)	*P*<0.00001	*P*<0.00001	*P*<0.00001	*P*=0.002	
N	49	53	56	55	56

Note. CRP = C reactive protein; Hb = hemoglobin; QOL = quality of life

Regression

For the regression model, fatigue was entered in as the dependent variable with hemoglobin and CRP as independent variables. Initially hemoglobin was entered first in the regression model. The model was rerun entering CRP in first with no difference in results. The regression model was rerun two further times using Energy level (FACT-F) and QOL as the dependent variables in each regression model.

Using Fatigue EORTC-QLQC30 as the DV, a significant model emerged (F=7.784, *P*=0.001). CRP was significant in predicting Fatigue EORTC-QLQC30 (beta =0.494, *P*=0.004) while hemoglobin was not significant (beta=-0.015, *P*=0.28). This

suggests that high CRP is associated with more fatigue and alternatively, low CRP is associated with less fatigue.

Similarly, using Energy level (FACT-F) as the DV, a significant model emerged (F=6.800, *P*=0.003). Again, CRP was a significant variable in predicting Energy level (FACT-F) (beta=-0.350, *P*=0.034) while hemoglobin was not (beta= 0.192, *P*=0.237). These results suggest that low CRP is associated with higher energy level while high CRP is associated with lower energy level.

Figures 7a, 7b, 8a, 8b, 9a and 9b are regression curves from the above analyses.

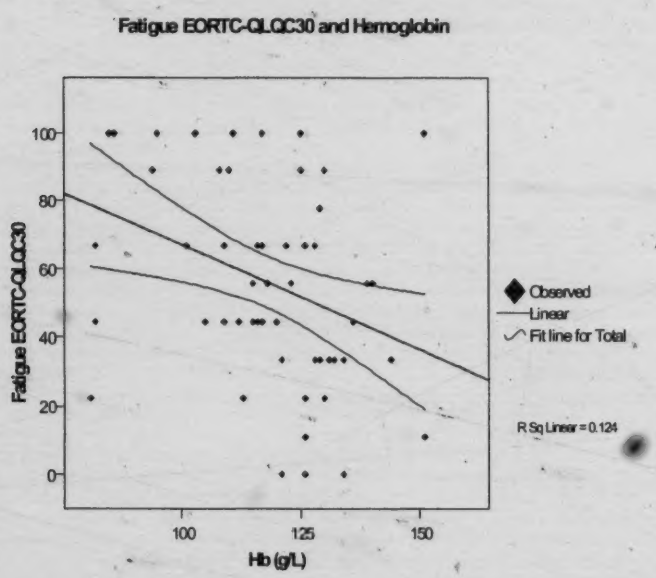

Figure 7a. Linear regression of Fatigue EORTC-QLQC30 and Hemoglobin

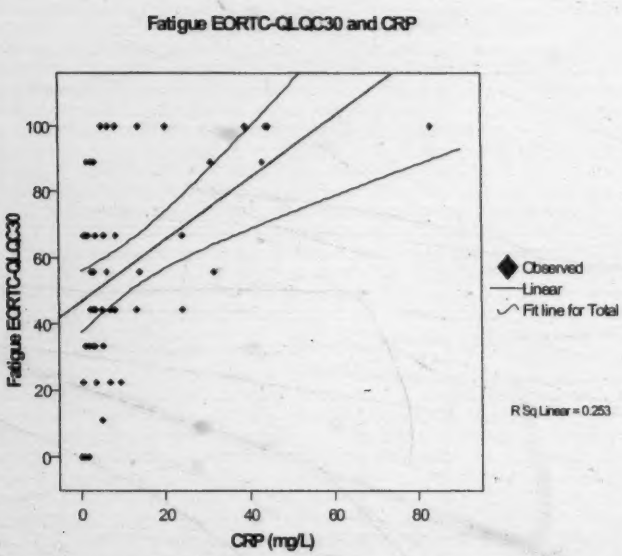

Figure 7b. Linear regression of Fatigue EORTC-QLQC30 and CRP

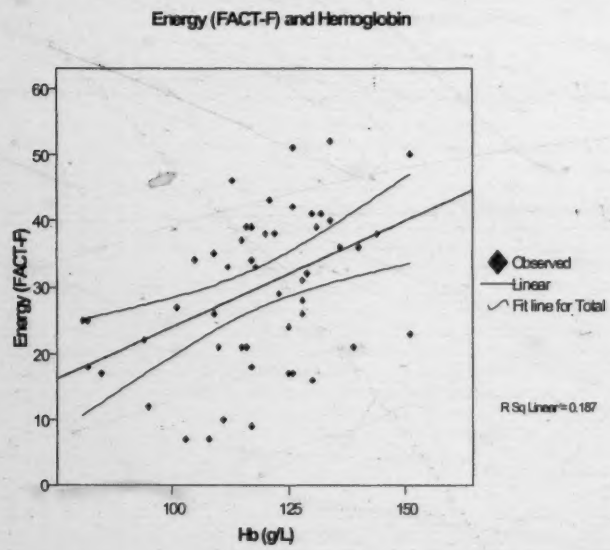

Figure 8a. Linear regression of Energy (FACT-F) and Hemoglobin

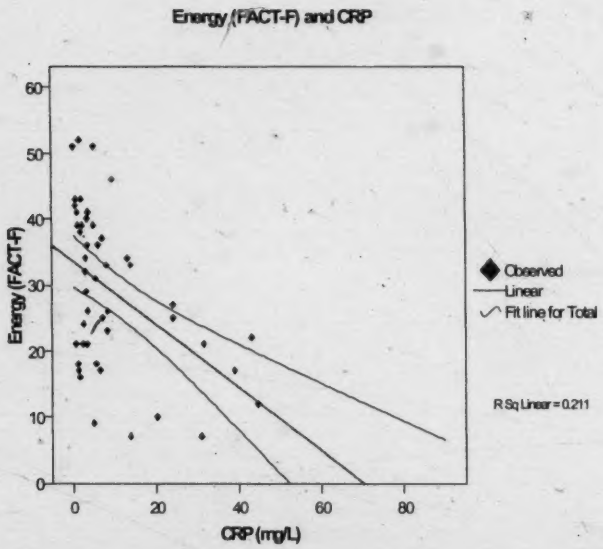

Figure 8b. Linear regression of Energy (FACT-F) and CRP

When QOL was used as the DV, the model was again significant (F=9.385, $P<0.00001$). CRP was a significant variable in predicting QOL (beta= -0.427, $P=0.010$) and hemoglobin was not (beta=0.157, $P=0.328$). This suggests that low CRP predicts better QOL and high CRP predicts worse QOL.

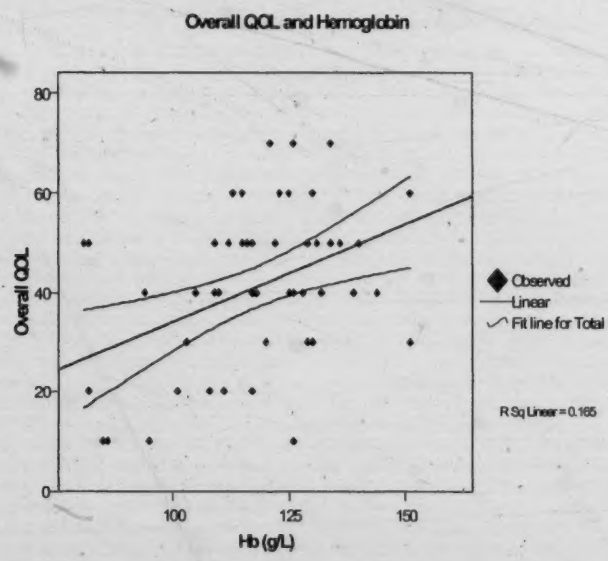

Figure 9a. Linear regression of Overall QOL and Hemoglobin

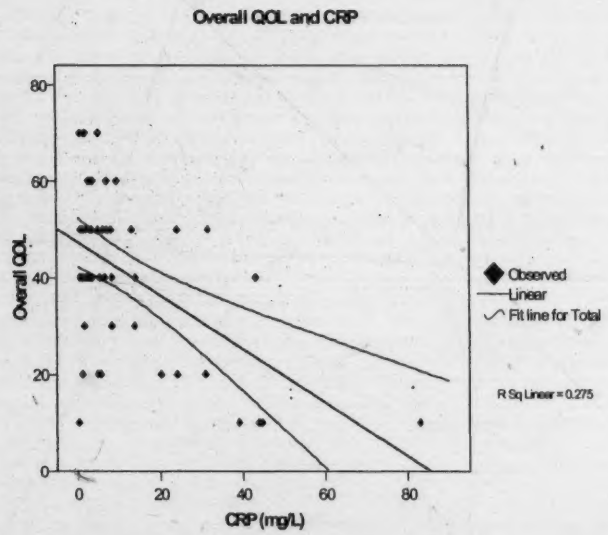

Figure 9b. Linear regression of Overall QOL and CRP

Summary of Findings

Study Sample

The demographic information obtained on the study participants is consistent with previous studies of patients with multiple myeloma with respect to age, gender, classification and stage. The prevalence of diabetes mellitus in individuals 60-74 years in Canada is 12.19% and increases to 13.49% in individuals ≥75 (Health Canada, 2002). The mean age in the sample is 61.96 years. The finding of 17.9% rate of previous appendectomy is interesting. Previous epidemiological studies have examined the associations between various medical conditions and the subsequent development of cancer (Cope et al., 2003). Of particular interest to researchers has been the hypothesized link between autoimmune conditions, infection/inflammation and the development of cancer. Studies examining the relationship between appendectomy and risk of cancer have reported mixed results. A Swedish study in 2003 identified increased risk for the

development of NHL and stomach cancer occurring after remote appendectomy though failed to find associations between appendectomy and other types of cancer (Cope et al.).

The pathophysiology is thought to be due to infection/inflammation of lymphoid tissue in addition to surgical removal of such tissue at a young age. The appendix is laden with lymphoid tissue that develops early in life and continues to grow into early adulthood. It is possible that the appendix contributes to immune function via gut-associated lymphoid tissue (GALT). An epidemiological study in 1990 reported a lifetime risk of appendicitis of 8.6% for males and 6.7% for females (Addiss, Shaffer, Fowler & Tauxe, 1990). The lifetime risk of appendectomy was 12% for males and 23.1% for females. By gender, 26.9% of the women in the sample had a history of appendectomy while 10% of the men in the sample had previous appendectomy. Without an age-matched control group, the clinical significance of this finding is difficult to interpret.

Study Variables

The average hemoglobin in this cohort of patients was 117.73g/L. There was a statistically significant relationship between gender and hemoglobin (r=0.317, *P*=0.018) and gender and Energy [(FACT-F), r=0.290, *P*=0.035]. Being male was associated with having more energy (less fatigue). The relationship between gender and hemoglobin has been documented in the literature (Stasi, Abriani, Beccaglia, Terzoli, & Amadori, 2003; Prue, Rankin, Allen, Gracey, & Cramp, 2006). Physiologic and metabolic differences between women and men result in discrepant average normal hemoglobin levels. The relationships between gender and CRP (r=-0.209, *P*=0.149), gender and fatigue [(Fatigue

EORTC-QLQC30) r=-0.206, *P*=0.128], and gender and QOL (r=0.172, *P*=0.205) were not statistically significant.

The lack of relationships between stage of disease and fatigue and stage of disease and QOL has been reported in previous studies. In their appraisal of literature on cancer-related fatigue, Prue et al. (2006) reported seven studies that found no relationship between fatigue and tumor stage and three studies that did demonstrate a relationship between fatigue and tumor stage. Additionally, they found one study with no reported relationship between fatigue and time since diagnosis. In this study, there was no relationship between fatigue and time since diagnosis and no relationship between QOL and time since diagnosis.

The correlations between hemoglobin, fatigue and QOL were not surprising. To date, much of the research on fatigue has focused on the association between anemia and fatigue. The highly significant relationships that emerged between CRP, fatigue and QOL are intriguing. These results suggest that higher CRP is predictive of greater fatigue, less energy and lower QOL. There is growing support in the literature for the role of cytokines in inducing cancer related symptoms.

Regression analyses were carried out three times, using Fatigue EORTC-QLQC30, Energy (FACT-F) and QOL as dependent variables. When fatigue was entered as the dependent variable and CRP and hemoglobin as independent variables, the model was significant (*P*=0.001) and suggested hemoglobin was not predictive of patient reported fatigue once the effect of inflammation (as measured by CRP) was taken into account. When Energy was entered as the dependent variable and CRP and hemoglobin as independent variables, the model was significant (*P*=0.003) and as above, suggested

that hemoglobin was not predictive of patient reported energy once CRP was taken into account. Similarly, when QOL was entered as the dependent variable with CRP and hemoglobin entered as independent variables, the regression model was again significant ($P<0.00001$) and suggested that hemoglobin was not predictive of patient reported QOL once the effect of inflammation was taken into account.

These results support the research hypothesis that hemoglobin is not a significant predictor of fatigue or QOL in individuals with MM once the effect of inflammation is accounted for. The null hypothesis that anemia is the exclusive predictor of fatigue and QOL can therefore be rejected.

Chapter 5: Discussion

It is becoming increasingly more apparent that fatigue is symptom mediated peripherally as well as centrally (Gutstein, 2001). Cytokines and chemokines act on peripheral nerves and directly in the brain to induce various effects of sickness response (Illman et al., 2005). In particular, IL-1, TNF-α, IL-6 and IFN are released by activated immunocytes. Glutamate, nitric oxide, prostaglandins and substance P act in the brain including the paraventricular nucleus of the hypothalamus and amygdala (Illman et al.). Neurotransmitters such as serotonin, dopamine and norepinephrine are affected. The hypothalamic-pituitary-adrenal (HPA) axis is activated and this leads to upregulation of plasma concentration of corticosteroids. The resulting symptoms include fatigue, pain, muscle wasting, cognitive impairment, anxiety and depression (Illman et al.).

Proinflammatory cytokines are known to blunt the erythropoietin response to low hemoglobin as well impair erythroid colony formation in response to erythropoietin (Maccio et al., 2005). In their study of patients with untreated ovarian cancer, Maccio et

al. found that IL-6 and stage of disease were independent factors in predicting hemoglobin levels. Additionally, recombinant human IL-6 (rhIL-6) has been found to induce anemia. During a phase II trial where 15 patients received rhIL-6 as treatment for metastatic renal cell carcinoma, hemoglobin decreased within three days after the initiation of therapy (Nieken et al., 1995). C-reactive protein, α1-antitrypsin and serum amyloid increased while transferrin decreased (Nieken et al.). Other researchers have reported the association between IL-6 and increased levels of CRP, serum amyloid A, fibrinogen, complement and α1-antitrypsin (Ershler, 2003). Further, elevated levels of IL-6 are associated with greater functional impairment, depression and increased mortality.

Anti IL-6 monoclonal antibodies have been used to treat patients with multiple myeloma (Trikha et al., 2003). In a study of patients with MM who received anti-IL-6 monoclonal antibody therapy, outcomes included inhibition of CRP synthesis, decrease in hypercalcemia, reduction in fever and reduced tumor mass (Moreau et al., 2000). The reduction in CRP was correlated with a high rate of complete response.

This study identified negative correlations between hemoglobin and fatigue and positive correlations between hemoglobin and QOL. These findings are consistent with previous studies (Ludwig et al., 2002; Holzner et al., 2002; Palumbo et al., 2004; Prue et al., 2006). Patients with MM may have anemia for a variety of reasons including disease involvement, myelosuppressive treatment, nutritional deficiencies, anemia/chronic disease and/or comorbid medical conditions. It is reasonable to consider that anemia may contribute to fatigue in this patient population. Wisloff, Gulbrandsen, Hjorth, Lenhoff, & Fayers (2005) examined the relationship between hemoglobin and fatigue and hemoglobin and QOL in patients with MM. Though they found a statistically significant

relationship between hemoglobin and fatigue, their regression model suggested that the ability to predict fatigue from hemoglobin level was low. Further, when multivariate analysis was conducted on data collected at 12 months follow-up, the relationship between hemoglobin and fatigue was only of borderline statistical significance (Wisloff et al., 2005).

Previous studies have found associations between fatigue and various hematological or biochemical variables such as hemoglobin, hematocrit, albumin, thyroid hormone (Cella, Kallich, McDermott & Xu, 2004; Dimeo et al., 2004; Knight et al., 2004; Wang et al., 2002). Perhaps the most widely studied relationship is that between hemoglobin and fatigue. Certainly may authors have identified positive correlations between low hemoglobin and fatigue or alternatively, between high hemoglobin and reduction of fatigue. However, these relationships have been inconsistent and do not explain the high prevalence of fatigue in patients who are not anemic (Prue et al., 2006). For example, breast cancer patients undergoing radiotherapy have reported high levels of fatigue in the absence of anemia (Ahlberg, Ekman, & Gaston-Johansson, 2004). Additionally, though few in number, studies examining fatigue in cancer survivors report high levels of fatigue even years after treatment completion (Bower et al., 2000; Prue et al.). This has led to increasing recognition that anemia is not the only cause of fatigue in patients with cancer (Cella et al., 2004; Holzner et al., 2002; Schubert, Hong, Natarajan, Mills, & Dimsdale, 2006; Stone, Richards, A'Hern & Hardy, 2000).

The finding in this study that anemia was not a significant predictor of fatigue or QOL once the effect of inflammation was accounted for is novel and suggests that an alternative process may be involved in the development of cancer-related fatigue and

QOL. The positive correlation demonstrated between CRP and fatigue and negative correlation between CRP and QOL in patients with MM is also a novel finding. Previous authors have identified elevated CRP levels in fatigued cancer patients (Brown et al., 2005; Maccio et al., 2005; Wratten et al., 2004) though none have studied this relationship in patients with MM. Both IL-6 and CRP are implicated in inflammatory processes and both have been found to be elevated or dysregulated in patients with MM (Durie et al. 2003; Hideshima et al., 2004; VanZaanen et al., 1998). More specifically, CRP is an IL-6-induced acute phase protein (Illman et al., 2005).

Cancer and its treatment are associated with the release of inflammatory markers by immune cells and malignant cells (Schubert et al., 2006). Further, the finding that symptoms such as fatigue, fever, depressed activity and anorexia are induced by the infusion of cytokines has led both clinicians and researchers to speculate about the role of cytokines in the development of these symptoms. In addition to influencing subjective symptoms, cytokines such as IL-6 and TNF have also been found to interfere with red blood cell production. It is possible that the contributions of cytokines to the development of fatigue may be direct or indirect as in the genesis of anemia, which could then contribute, at least in part, to fatigue.

Though it remains an evolving field of research, the contribution of inflammatory mediators to the development of cancer-related fatigue has been investigated by researchers. In a review of 20 published studies on the relationships between fatigue and inflammatory makers in cancer patients, Schubert et al.(2006) reported that while many of the individual studies failed to demonstrate a relationship between cytokines and cancer-related fatigue, pooled analysis of all correlations resulted in overall significantly

positive associations between cancer-related fatigue and inflammatory makers. The studies were heterogeneous with respect to cancer and treatment type, fatigue questionnaire used and type of inflammatory marker(s) measured.

Importantly, the aberrant production or expression of cytokines varies with type of cancer diagnosis (Schubert et al., 2006). An advantage of this study is that it involved a homogenous group of patients as far as diagnosis is concerned. C-reactive protein has been found to be elevated in patients with MM (Durie et al., 2003). Studying the relationship between CRP and the development of fatigue in this particular patient population may explain why CRP was found to be a significant predictor of fatigue in this study while previous studies with heterogeneous samples have failed to identify such a relationship.

Nursing Implications

Practice

Nurses are involved in and play a pivotal role in the assessment and management of cancer-related fatigue (Wood, Nail, Gilster, Winters & Elsea, 2006). As a greater understanding of the mechanisms underlying fatigue emerges, potential targets for therapy will also emerge. Current fatigue management strategies can be divided into correcting underlying pathology such as low hemoglobin or nutritional deficiencies (folate, vitamin B12, iron), counseling on various lifestyle modification factors such as sleep hygiene, stress management and adequate exercise (Illman et al., 2005; Olson, Krawchuk, & Quddusi, 2007; Stasi et al., 2003).

Correction of anemia generally occurs through blood transfusions for severe anemia and through the use of erythropoietic stimulating agents (ESAs) such as epoetin

alfa and darbepoetin alfa for anemia not requiring immediate intervention. Epoetin alfa and darbepoetin alfa are recombinant human erythropoietin agents licensed for the treatment of anemia in cancer patients with non-myeloid malignancies (Stasi et al., 2005). These drugs have been found to decrease the transfusion requirements of patients as well as lead to improvements in QOL and reductions in patient-reported fatigue (Stasi et al., 2005). Nonetheless, 30-50% of cancer patients treated with ESAs do not respond to these agents (Henry, Dahl, Auerbach, Tchekmedyian & Laufman, 2007).

The discovery that increased IL-6 upregulates the hepatic production of hepcidin may represent a potential target for treating anemia in patients with MM (Cucuianu, Patiu, & Rusu, 2006). More specifically, when hepcidin binds to ferroportin, anemia results due to the blockage of iron export from enterocytes and macrophages. The use of new targeted therapies for the treatment of anemia may benefit patients with MM. Nonetheless, as the relationship between anemia and cancer-related fatigue has not yet been clearly established, correction of underlying anemia may be an inadequate intervention for fatigue (Bohlius et al., 2006; Morrow, Shelke, Roscoe, Hickok, & Mustian, 2005).

Control of concomitant symptoms is an integral component of fatigue management (Wagner & Cella, 2004). Many patients are unable to sleep due to uncontrolled pain, nausea, vomiting or diarrhea. Unfortunately, many of the medications used to treat cancer and its associated symptoms induce side effects themselves that may lead to impaired sleep, increased drowsiness, somnolence and psychogenic symptoms such as anxiety or agitation. The use of stimulants such as methylphenidate and dextroamphetamine have been tried with some success in patients though there are no

controlled trials examining these agents in patients with cancer related fatigue (Burks, 2001; Morrow et al., 2005; Stasi et al., 2003). These agents have the potential to cause appetite suppression and insomnia which may subsequently exacerbate the patient's fatigue (Burks; Stasi et al.). Glucocorticoids have also been efficacious in the treatment of fatigue but are known to cause various side effects such as agitation, insomnia, gastrointestinal discomfort and adrenal insufficiency (Morrow et al., 2005). Ensuring that comorbid medical conditions like depression and thyroid dysfunction are controlled may also lead to reduction in fatigue (Wagner & Cella).

Research

Further research on the etiology of fatigue is clearly warranted. In particular, the identification of processes or substances involved in the development of fatigue may lead to improved treatment strategies and ultimately, reduction in cancer-related fatigue and improvement in QOL. Long-term studies assessing correlates of fatigue in patients throughout the illness trajectory are needed. Assessing correlates of fatigue in patients with no active disease or those with stable disease who are not receiving treatment may help to clarify the factors involved in the development of cancer-related fatigue.

Novel therapies for fatigue.

As fatigue represents a symptom with multiple etiological factors, multidisciplinary approaches to research and intervention are needed. Combined efforts of nurses with physicians, pharmacists, psychologists, nutritionists, physiotherapists and occupational therapists will contribute to holistic assessment and intervention of cancer-related fatigue. Research examining the efficacy of non-pharmacologic interventions such as stress management, attention to diet and exercise is ongoing.

Immunologic agents.

Trials testing cytokine antagonists as cancer therapy have serendipitously found that many of these agents are effective in reducing patients' symptoms and improving quality of life. In their review of anti-IL-6 monoclonal antibody therapy for cancer, Trikha et al. (2003) report that such therapy was generally well tolerated and resulted in improvements in cancer-related symptoms such as pain, fever and cachexia. While the ultimate clinical significance of these agents with respect to controlling disease remains to be established, the authors suggest that an additional outcome may be reduction in cancer-related symptoms (Trikha et al.).

Anti-inflammatory therapy.

This study found that inflammation was associated with fatigue in patients with multiple myeloma. Future research should explore whether anti-inflammatory therapy may be useful in reducing CRP and fatigue. In particular, non-steroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin synthesis through cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). NSAIDs inhibit prostaglandin synthesis by blocking the constitutive cyclooxygenase (COX-1) enzyme.

Cyclooxygenase-2 is an enzyme required for prostaglandin synthesis in inflamed tissue and has been implicated both as a growth factor and poor prognostic factor in several cancers. In their study of COX-2 in patients with multiple myeloma, Ladetto et al. (2005) found that COX-2 expression was related to disease progression, expressed by malignant plasma cells and was an independent predictor of poor outcome. In certain conditions and under certain circumstances, COX-2 is induced. Like COX-1, this enzyme has a role in the metabolism of arachadonic acid to prostaglandin E2 which

then stimulates angiogenesis. More specifically, COX-2 is an enzyme required for the metabolism of arachadonic acid to prostaglandin E_2 which then stimulates angiogenesis (Prince et al., 2005). Interleukin 6 production is influenced by IL-1β through a prostaglandin E2 loop.

Ladetto et al. (2005) suggest that inhibition of COX-2 may contribute therapeutically to the control of multiple myeloma as part of maintenance therapy or in combination with other medications (Ladetto). Indeed, others have reported that selective inhibition of COX-2 impedes angiogenesis, stimulates apoptosis and decrease metastases in both *in vitro* and *in vivo* tumor models (Prince et al., 2005). In their phase II multicenter trial of thalidomide and celecoxib in patients with relapsed and refractory multiple myeloma, Prince et al. found that the addition of high dose celecoxib added to the antitumor activity of thalidomide with some improvements in response rates, progression free survival and overall survival. The combination of thalidomide and high dose celecoxib, however, resulted in significant toxicity and further study is required to evaluate the efficacy and safety of these agents in combination. Recently, there has been concern over the use of COX-2 inhibitors and significant cardiovascular events (Gislason et al., 2006; Mathieu, Meier, Meier, Starten, & Burnier, 2005).

Education

The prevalence of fatigue experienced by patients in this study highlights the importance of educating nurses and members of the allied health care team about fatigue assessment and management. The findings in this study suggest that interventions for fatigue must extend beyond the correction of anemia. As correction of anemia has been of the most common interventions employed to treat cancer-related fatigue in the past,

communicating the findings of this study to nurses and other health care professionals may improve assessment and open the door for novel interventions.

In addition to nursing education, great opportunity exists for patient education with respect to fatigue and its management. Encouraging patients to report their fatigue to members of the treatment team is an important element of patient education. It has been reported that patients are often hesitant to discuss their fatigue with physicians as they fear their treatment may be altered (NCCNa, 2007). Additionally, many patients do not recognize the severity of fatigue as its onset can often be insidious. Many patients expect fatigue as part of their cancer diagnosis or treatment and are not aware that anything can be done to treat it.

Policy

The development and implementation of fatigue management guidelines is essential. The National Comprehensive Cancer Network (NCCNa) recommends that patients should routinely be screened for fatigue and both assessment and management should be supported by clinical practice guidelines developed by interdisciplinary committees (NCCNa, 2007). Assessment and intervention should occur at diagnosis and at regular intervals thereafter. The addition of cancer-related fatigue as an outcome measure in clinical studies is suggested by NCCN as is the inclusion of fatigue management to institutional quality improvement projects (NCCNa). Patient education is considered an integral aspect of fatigue management from time of diagnosis onward.

Limitations of Study

The non-probability sampling strategy in this study may have led to selection bias, and influenced the study results by limiting generalizability. This study employed a cross-sectional design, only capturing patients' symptoms and clinical variables at one time point. Assessing the trends of variables over time, throughout the illness and treatment trajectories, would likely provide valuable data on patterns of fatigue and relationships with clinical parameters.

Fatigue is influenced by numerous physiologic and psychosocial variables. There may have been additional factors contributing to fatigue and QOL in this study that were not assessed. For example, information was not obtained on patients' exercise level or nutritional status. Further, the impact of psychosocial variables such as marital status, relationships, employment status, financial stress and subclinical anxiety/depression was not examined. The variability in the sample with respect to previous and current treatment regimens may have also been a confounder in this study. C-reactive protein was used as a marker of inflammation in this study. While CRP is indicative of inflammation, it is a relatively non-specific marker. There may have been substantial heterogeneity among patients with respect to the etiology of CRP level.

Chapter 6: Conclusion

The prevalence of fatigue in this population of patients with multiple myeloma supports a role for ongoing assessment and management of fatigue. It is apparent that numerous factors contribute to the development of fatigue and as such, nurses must take a comprehensive approach to fatigue assessment and management. While much of the literature to date has focused on the role of anemia in cancer-related fatigue, the findings

in this study support an alternative process in the development of fatigue in patients with multiple myeloma and highlight the importance of exploring novel treatments for cancer-related fatigue. Through ongoing assessment and involvement in the management of cancer-related fatigue nurses have the opportunity to positively influence patient QOL and reduce the morbidity associated with cancer-related symptoms.

Further research exploring the pathophysiology of fatigue is clearly warranted. Such research will not only help to characterize a highly variable and subjective symptom but may also unearth potential targets for therapy. The management of other cancer-related symptoms including chemotherapy-induced nausea and pain has benefited greatly in recent years due to greater understanding of the pathogenic mechanisms involved in each symptom. The introduction of $5HT_3$ antagonists has revolutionized management of nausea related to chemotherapy. Similarly, greater understanding of the pathology of pain and the distinction of various types of pain as nociceptive or neuropathic has led to dramatic improvements in pain management. Though fatigue is a complex symptom with numerous potential etiological factors, its ubiquitous presence in the lives of cancer patients emphasizes the need for unfailing assessment and intervention with the goal of reducing morbidity and increasing quality of life in patients with cancer.

References

Aaronson, N.K., Ahmedzai, S., Bergman, B., Bullinger, M., Cull, A., Duez, N.J., et al. (1993). The European Organization for Research and Treatment of Cancer QLQC30: A quality of life instrument for use in international clinical trials in oncology. *Journal of the National Cancer Institute, 85*(5), 365-376.

Addiss, D.G., Shaffer, N., Fowler, B.S., & Tauxe, R.V. (1990). The epidemiology of appendicitis and appendectomy in the United States. *American Journal of Epidemiology, 132,* 910-925.

Ahlberg, K., Ekman, T., & Gaston-Johansson, F. (2004). Levels of fatigue compared to levels of cytokines and hemoglobin during pelvic radiotherapy: A pilot study. *Biological Research for Nursing, 5*(3), 203-210.

Ahlberg, K., Ekman, T., Gaston-Johansson, F., & Mock, V. (2003). Assessment and management of cancer-related fatigue in adults. *Lancet*Retrieved November 30, 2005, from: http://image.thelancet.com/extras/02art6023web.pdf

Alberta Cancer Board. (2004). *Research protocol approval application for science and ethics.* Retrieved August 10, 2004, from: www.cancerboard.ab.ca

Andrews, N.C. (2004). Anemia of inflammation: The cytokine-hepcidin link. *Journal of Clinical Investigation, 113*(9), 1251-1253.

Attal, M., Harousseau, J.L., Facon, T., Guilhot, F., Doyen, C., Fuzibet, J.G., et al. (2003). Single versus double autologous stem-cell transplantation for multiple myeloma. *New England Journal of Medicine, 349,* 2495-2502.

Attal, M., Harousseau, J.L., Stoppa, A.M., Sotto, J.J., Fuzibet, J.G., Rossi J.F., et al.

(1996). A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. *New England Journal of Medicine, 335,* 91-97.

Avet-Loiseau, H., Attal, M., Moreau, P., Charbonnel, C., Garban, F., Hulin, C., et al. (2007). Genetic abnormalities and survival in multiple myeloma: The experience of the Intergroupe Francophone du Myelome. *Blood First Edition Paper.* Retrieved February 20, 2007 from: http://bloodjournal.hematologylibrary.org/cgi/content/abstract/blood-2006-08-040410v1

Barlogie, B., Kyle, R.A., Anderson, K.C., Greipp, P.R., Lazarus, H.M., Hurd, D.D., et al. (2006). Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: Final results of Phase III US Intergroup Trial S9321. *Journal of Clinical Oncology, 24*(6), 929-936.

Barlogie, B., Tricot, G., Rasmussen, E., Anaissie, E., van Rhee, F., Zangari, M., et al. (2005). Total therapy 3 (TT3) incorporating Velcade (V) into upfront management of multiple myeloma: Comparison with TT2 + Thalidomide (T). *Blood, 106,* 1154 (ASH Annual Meeting Abstracts).

Barnes, E.A., & Bruera, E. (2002). Fatigue in patients with advanced cancer: A review. *International Journal of Gynecological Cancer, 12*(5), 424-428.

Bataille, R., Barlogie, B., Lu, Z.Y., Rossi, J.F., Lavabre-Bertrand, T., Beck, T., et al. (1995). Biologic effects of anti interleukin-6 murine monoclonal antibody in advanced multiple myeloma. *Blood, 86,* 685-691.

Bohlius J, Wilson J, Seidenfeld, J, Piper M, Schwarzer G, Sandercock J, et al. (2006).

Recombinant human erythropoietins and cancer patients: Updated meta-analysis of 57 studies including 9353 patients. *Journal of the National Cancer Institute, 98*, 708-714.

Blade, J. (2003). Transplantation for multiple myeloma: Who, when, how often? *Blood, 102*(10), 3469-3477.

Blade, J., Rosinol, L., Sureda, A., Ribera, J.M., Diaz-Mediavilla, J., Garcia-Larana, J., et al. (2005). High-dose therapy intensification compared with continued standard chemotherapy in multiple myeloma patients responding to the initial chemotherapy: Long-term results from a prospective randomized trial from the Spanish cooperative group PETHEMA. *Blood, 106*(12), 3755-3759.

Bower, J.E., Ganz, P.A., Desmond, K.A., Rowland, J.H., Meyerowitz, B.E., & Belin, T.R. (2000). Fatigue in breast cancer survivors: Occurrence, correlates, impact on quality of life. *Journal of Clinical Oncology, 18*(4), 743-753.

Brown, D.J., McMillan, D.C., & Milroy, R. (2005). The correlation between fatigue, physical function, the systemic inflammatory response and psychological distress in patients with advanced cancer. *Cancer, 103,* 377-382.

Bruno, B., Rotta, M., Patriarca, F., Mordini, N., Allione, B., Carnevale-Schianca, F., et al. (2007). A comparison of allografting with autografting for newly diagnosed myeloma. *New England Journal of Medicine, 356,* 1110-1120.

Burks, T.F. (2001). New agents for the treatment of cancer-related fatigue. *Cancer, 92*(s6), 1714-1718.

Canadian Cancer Society/National Cancer Institute of Canada. (2006). *Canadian Cancer Statistics 2006.* Toronto, ON: Author.

Cavenagh, J., Popat, R., Curry, N., Stec, J., Morris, T., Drake, M., et al. (2004). PAD combination therapy (PS-341/bortezomib, adriamycin and dexamethasone) for previously untreated patients with multiple myeloma. *Blood, 104,* 207 (ASH Annual Meeting Abstracts).

Cavo, M., & Baccarani, M. (2006). The changing landscape of myeloma therapy. *New England Journal of Medicine, 354*(10), 1076-1078.

Cavo, M., Cellini, C., & Zamagni, E. (2005). Update on high dose therapy – Italian Studies. *Haematologica, 90,* abstract PL8.04.

Cella, D., Kallich, J., McDermott, A., & Xu, X. (2004). The longitudinal relationship of hemoglobin, fatigue and quality of life in anemic cancer patients: Results from five randomized clinical trials. *Annals of Oncology, 15,* 979-986.

Chang, V.T., Thaler, H.T., Polyak, T.A., Kornblith, A.B., Lepore, J.M., & Portenoy, R.K. (1998). Quality of life and survival: The role of multidimensional symptom assessment. *Cancer, 83,* 173-179.

Child, J.A., Morgan, G.J., Davies, F.E., Owen, R.G., Bell, S.E., Hawkins, K., et al. (2003). High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. *New England Journal of Medicine, 348,* 1875-1883.

Cohen, J. (1977). *Statistical power analysis for the behavioral sciences (Revised Ed.).* New York, NY: Academic Press.

Cope, J.U., Askling, J., Gridley, G., Mohr, A., Ekbom, A., Nyren, O., et al. (2003). Appendectomy during childhood and adolescence and the subsequent risk of cancer in Sweden. *Pediatrics, 111*(6), 1343-1350.

Cottler-Fox, M.H., Lapidot, T., Petit, I., Kollet, O., DiPersio, J.F., Link, D., et al. (2003).

Stem cell mobilization. *Hematology,* 419-437.

Cucuianu, A., Patiu, M., & Rusu, A. (2006). Hepcidin and multiple myeloma related anemia. *Medical Hypotheses, 66*(2), 352-354.

Dimeo, F., Schmittel, A., Fietz, T., Schwartz, S., Kohler, P., Boning, D., et al. (2004). Physical performance, depression, immune status and fatigue in patients with hematological malignancies after treatment. *Annals of Oncology, 15,* 1237-1242.

Durie, B.G., Harousseau, J.L., Miguel, J.S., Blade, J., Barlogie, B., Anderson, et al. (2006).International uniform response criteria for multiple myeloma. *Leukemia, 20,* 1467-1473.

Durie, B.G., Kyle, R.A., Belch, A., Bensinger, W., Blade, J., Boccadoro, M. et al. (2003). Myeloma management guidelines: A consensus report from the Scientific Advisors of the International Myeloma Foundation. *The Hematology Journal, 4,* 379-398.

Earlam, S., Glover, C., Fordy, C., Burke, D., & Allen-Mersh, T.G. (1996). Relation between tumor size, quality of life, and survival in patients with colorectal liver metastases. *Journal of Clinical Oncology, 14,* 171-175.

Ershler, W.B. (2003). Biological interactions of aging and anemia: A focus on cytokines. *Journal of American Geriatrics Society, 51,* S18-S21.

European Organization for Research and Treatment of Cancer. (2005). *EORTC Quality of Life Questionnaires.* Retrieved September 20, 2005 from: http://www.eortc.be/home/qol/ExplQLQC30.htm

Fassas, A.B., Van Rhee, F., & Tricot, G. (2003). Predicting long-term survival in

multiple myeloma patients following autotransplantation. *Leukemia and Lymphoma, 44,* 749-758.

Fermand, J.P. (2005). High dose therapy supported with autologous blood stem cell transplantation in multiple myeloma: Long term follow up of the prospective studies of the MAG group. *Haematologica, 90,* 40 PL8.05.

Fermand, J.P., Katsahian, S., Divine, M., Leblond, V., Dreyfus, F., Macro, M., et al. (2005). High-dose therapy and autologous blood stem-cell transplantation compared with conventional treatment in myeloma patients aged 55 to 65 years: Long-term results of a randomized control trial from the Group Myeloma-Autogreffe. *Journal of Clinical Oncology, 23*(36), 9227-9233.

Fonseca, R., Barlogie, B., Bataille, R., Bastard, C., Bergsagel, P.L., Chesi, M., et al. (2004). Genetics and cytogenetics of multiple myeloma. *Cancer Research, 64,* 1546-1558.

Garban, F., Attal, M., Michallet, M., Hulin, C., Bourhis, J.H., Yakoub-Agha, I., et al. (2006). Prospective comparison of autologous stem cell transplantation followed by dose-reduced allograft (IFM99-03 trial) with tandem autologous stem cell transplantation (IFM99-04 trial) in high-risk de novo multiple myeloma. *Blood, 107*(9), 3474-3480.

Gertz, M.A. (2004). Too old for transplantation: think again. *Blood, 104*(10), 3000-3001.

Gislason G.H., Jacobsen S., Rasmussen J.N., Rasmussen, S., Buch, P., Friberg J., et al. (2006). Risk of death or reinfarction associated with the use of selective cyclooxygenase-2 inhibitors and nonselective anti-inflammatory drugs after acute myocardial infarction. *Circulation, 113*(25), 2906-2913.

Goldschmidt, H. (2005). Single vs. double high-dose therapy in multiple myeloma: second analysis of the GMMG-HD2 Trial. *Haematologica, 90,* 38 PL8.02.

Greipp, P.R., San Miguel, J., Durie, B.G., Crowley, J., Barlogie, B., Blade, J. et al. (2005). International staging system for multiple myeloma. *Journal of Clinical Oncology, 23,* 3412-3420.

Gutstein, H.B. (2001). The biologic basis of fatigue. Cancer, *92,* 1678-1683.

Hari, P., Pasquini, M.C., & Vesole, D.H. (2006). Cure of multiple myeloma – more hype, less reality. *Bone Marrow Transplantation, 37*(1), 1-18.

Harousseau, J.L., Attal, M., Leleu, X., Gressin, R., Hulin, C., Fuzibet, J-G., et al. (2004). Bortezomib (Velcade) plus dexamethasone as induction treatment prior to autologous stem cell transplantation in patients with newly diagnosed multiple myeloma: Preliminary results of an IFM phase II study. *Blood, 104,* 1490 (ASH Annual Meeting Abstracts).

Harousseau, J.L., & Moreau, P. (2002). Prognostic factors in myeloma. In J. Mehta & S. Singhal (Eds.), *Myeloma* (pp. 169-183). London, England: Martin Dunitz Ltd.

Health Canada. (2002). *Diabetes in Canada. Second Edition.* Retrieved February 25, 2007 from: http://www.phac-aspc.gc.ca/publicat/dic-dac2/pdf/dic-dac2_en.pdf

Henry, D.H., Dahl, N.V., Auerbach, M., Tchekmedyian, S., & Laufman, L.R. (2007). Intravenous ferric gluconate significantly improves response to epoetin alfa versus oral iron or no iron in anemic cancer patients receiving chemotherapy. *The Oncologist, 12,* 231-242.

Hidalgo-Collado, A., Bower, J.E., Ganz, P.A., Cole, S.W. & Irwin, M.R. (2006).

Inflammatory biomarkers for persistent fatigue in breast cancer survivors. *Clinical Cancer Research, 12*(9), 2759-2766.

Hideshima, T., Bergsagel, P.L., Kuehl, W.M., & Anderson, K.C. (2004). Advances in the biology of multiple myeloma: Clinical applications. *Blood,* 104(3), 607-618.

Hideshima, T., Richardson, P.G. & Anderson, K.C. (2004). Novel therapies for multiple myeloma. In J.S. Malpas, D.E. Bergsagel, R.A. Kyle & K.C. Anderson (Eds.), *Myeloma Biology and Management* (pp.229-238). Philadelphia, PA: Saunders.

Hjermstad, M.J., Fayers, P.M., Bjordal, K., & Kaasa, S. (1998). Health-related quality of life in the general Norwegian population assessed by the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire: The QLQ-30. *Journal of Clinical Oncology, 16*(3), 1188-1196.

Hjermstad, M.J., Fossa, S.D., Bjordal, K., & Kaasa, S. (1995). Test-retest study of the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire. *Journal of Clinical Oncology, 13*(5), 1249-1254.

Holzner, B., Kemmler, G., Greil, R., Kopp, M., Zeimet, A., Raderer, M. et al. (2002). The impact of hemoglobin levels on fatigue and quality of life in cancer patients. *Annals of Oncology, 13,* 965-973.

Illman, J., Corringham, R., Robinson, D., Davis, H.M., Rossi, J.F., Cella, D. et al. (2005). Are inflammatory cytokines the common link between cancer associated cachexia and depression? *Journal of Supportive Oncology, 3*(1), 37-50.

Imamura, R., Miyamoto, T., Yoshimoto, G., Kamezaki, K., Ishikawa, F., Henzan, H., et

al., (2005). Mobilization of human lymphoid progenitors after treatment with granulocyte colony-stimulating factor. *Journal of Immunology, 175*(4), 2647-2654.

International Myeloma Foundation. (2004). *Concise review of the disease and treatment options. Multiple Myeloma.* North Hollywood, CA: Author.

Joshua, D.E., & Gibson, J. (2002). Epidemiology of plasma cell disorders. In J. Mehta & S. Singhal (Eds.), *Myeloma* (pp. 139-150). London, England: Martin Dunitz Ltd.

Jung, L., Holle, L., & Dalton, W.S. (2004). Discovery, development, and clinical applications of bortezomib. *Oncology, 18*(14 suppl), 4-13.

Kaasa, S., Bjordal, K., Aaronson, N., Moum, T., Wist, E., Hagen, S., et al. (1995). The EORTC Core Quality of Life Questionnaire (QLQC30): Validity and reliability when analyzed with patients treated with palliative radiotherapy.

Knight, K., Wade, S., & Balducci, L. (2004). Prevalence and outcomes of anemia in cancer: A systematic review of the literature. *American Journal of Medicine, 116*(7), 1-23.

Kurzrock, R. (2001). The role of cytokines in cancer-related fatigue. *Cancer, 92*(s6), 1684-1688.

Kyle, R.A., Morie, G.A., Witzig, T.E., Lust, J.A., Lacy, M.Q., Dispenzieri, A. et al. (2003). Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clinic Proceedings, 78,* 21-33.

Ladetto, M., Vallet, S., Trojan, A., Dell'Aquila, M., Montillo, L., Rosato, R., et al. (2004). Cyclooxygenase-2 (COX-2) is frequently expressed in multiple myeloma and is an independent predictor of poor outcome. *Blood, 105*(12), 4784-4791.

Lee, B.N., Dantzer, R., Langley, K.E., Bennett, G.J., Dougherty, P.M., Dunn, A.J., et al. (2004). A cytokine-based neuroimmunologic mechanism of cancer-related symptoms. *Neuroimmunomodulation, 11,* 279-292.

Lind, M., Vernon, C., Cruickshank, D, Wilkinson, P., Littlewood, T., Stuart, N. et al. (2002). The level of haemoglobin in anaemic cancer patients correlates positively with quality of life. *British Journal of Cancer, 86,* 1243-1249.

Lokhorst, H. (2002). Clinical features and diagnostic criteria. In J. Mehta & S. Singhal (Eds.), *Myeloma* (pp. 152-168). London, England: Martin Dunitz Ltd.

Ludwig, H., Pohl, G., & Osterborg, A. (2004). Anemia in multiple myeloma. *Clinical Advances in Hematology and Oncology, 2*(4), 233-241.

Ludwig, H., Rai, K., Blade, J., Dammacco, F., Degos, L., Itri, L., et al. (2002). Management of disease-related anemia in patients with multiple myeloma or chronic lymphocytic leukemia: Epoetin treatment recommendations. *The Hematology Journal, 3,* 121-130.

Maccio, A., Madeddu, C., Massa, D., Mudu, M.C., Lusso, M.R., Gramignano, G. et al. (2005). Hemoglobin levels correlate with interleukin-6 levels in patients with advanced untreated epithelial ovarian cancer: Role of inflammation in cancer-related anemia. *Blood, 106*(1), 362-367.

Martino, M., Console, G., Callea, V., Stelitano, C., Massara, E., Irrera, G., et al. (2007). Low tolerance and high toxicity of thalidomide as maintenance therapy after double autologous stem cell transplant in multiple myeloma patients. *European Journal of Haematology, 78*(1), 35-40.

Martino, M., Console, G., Irrera, G., Pratico, G., Stelitano, C., Callea, V., et al. (2006).

High-dose therapy and autologous peripheral blood stem cells transplantation followed by a very low reduced intensity regimen with fludarabine and cyclophsophamide and allograft improve complete remission rate in de novo multiple myeloma patients. *American Journal of Hematology, 81,* 973-978.

Mateos, M., Blade, J., Diaz, M., Lahuerta; J.J., Terol, M.J., Hernandez, J., et al. (2004). A phase I//II national, multi-center, open-label study of bortezomib plus melphalan and prednisone (V-MP) in elderly untreated multiple myeloma patients. *Blood, 104,* 3462 (ASH Annual Meeting Abstracts).

Mathieu, C., Meier, P., Meier, Z.U., Starten, A., & Burnier, M. (2005). Co-selective COX-2 inhibitors have adverse renal and cardiovascular effects? *Schweiz Rundsch Med Prax, 94*(47): 1851-1858.

Mazhar, D., Gillmore, R., & Waxman, J. (2005). COX and cancer. *QJM: An International Journal of Medicine, 98,* 711-718.

Moreau, P., Harousseau, J-L., Wijdenes, J., Morineau, N., Milpied, N. et al. (2000). A combination of anti-interleukin 6 murine monoclonal antibody with dexamethasone and high-dose melphalan induces high complete response rates in advanced multiple myeloma. *British Journal of Haematology, 109*(3), 661-664.

Morris, C., Iacobelli, S., Brand, R., Bjorkstrand, B., Drake, M., Niederwieser, D., et al., (2004). Benefit and timing of transplantations in multiple myeloma: Clinical findings and methodological limitations in a European Group for Blood and Marrow Transplantation Registry Study. *Journal of Clinical Oncology, 22*(9), 1674-1681.

Morrow, G.R., Andrews, P.L., Hickok, J.T., Roscoe, J.A., & Matteson, S. (2002). Fatigue

associated with cancer and its treatment. *Supportive Care in Cancer, 10,* 389-398.

Morrow, G.R., Shelke, A.R., Roscoe, J.A., Hickok, J.T., Mustian, K. (2005).Management of cancer-related fatigue. *Cancer Investigation, 23*, 229-239.

Multiple Myeloma Research Foundation. (2004). *Multiple Myeloma: A treatment overview.* New Canaan, CT: Author.

National Comprehensive Cancer Network. (2007a). Cancer-related fatigue. In *NCCN Clinical Practice Guidelines in Oncology™.* Retrieved March 27, 2007 from: http://www.nccn.org/professionals/physician_gls/PDF/fatigue.pdf

National Comprehensive Cancer Network. (2007b). Cancer-and treatment-related anemia. Retrieved March 27, 2007 from: http://www.nccn.org/professionals/physician_gls/PDF/anemia.pdf

National Comprehensive Cancer Network. (2007c). Multiple Myeloma. In *NCCN Clinical Practice Guidelines in Oncology™.* Retrieved March 27, 2007 from: http://www.nccn.org/professionals/physician_gls/PDF/myeloma.pdf

Nieken, J., Mulder, N.H., Buter, J., Vellenga, E., Limburg, P.C., Piers, D.A., & de Vries, E.G. (1995). Recombinant human interleukin-6 induces a rapid and reversible anemia in cancer patients. *Blood, 86,* 3, 900-905.

Nemeth, E., Rivera, S., Gabayan, V., Keller, C., Taudorf, S., Pedersen, B.K., et al. (2004). IL-6 mediates hypoferremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin. *Journal of Clinical Investigation, 113*(9), 1271-1276.

Offidani, M., Corvatta, L., Piersantelli, M.N., Visani, G., Alesiani, F., Brunori, M., et al.

(2006). Thalidomide, dexamethasone, and pegylated liposomal doxorubicin (ThaDD) for patients older than 65 years with newly diagnosed multiple myeloma. *Blood, 108*(7), 2159-2164.

Olson, K., Krawchuk, A., & Quddusi, T. (in press). Fatigue in individuals with advanced cancer in active treatment and palliative settings. *Cancer Nursing.*

Olson, K., & Morse, J. (2005). Delineating the concept of fatigue using a pragmatic utility approach. In J. Cutcliff and H. McKenna (Eds.). The essential concepts of nursing (pp. **xx-yy).** Oxford, UK: Elsevier, Science.

Orlowski, R.Z. (2006). Initial therapy of multiple myeloma patients who are not candidates for stem cell transplantation. *Hematology*, 338-347.

O'Shea, D., Giles, C., Terpos, E., Perz, J., Politou, M., Sana, V., et al. (2006). Predictive factors for survival in myeloma patients who undergo autologous stem cell transplantation: A single-center experience in 211 patients. *Bone Marrow Transplantation, 37,* 731-737.

Palumbo, A., Bertola, A., Musto, P., Caravita, T., Callea, V., Cangialosi, C., et al. (2004). A prospective randomized trial of oral melphalan, prednisone, thalidomide (MPT) vs oral melphalan and prednisone (MP): An interim analysis. *Blood, 104,* 207 (ASH Annual Meeting Abstracts).

Palumbo, A., Falco, P., Baldini, L., Barbui, A., Benedetti, E., Bergonzi, C., et al. (2002). Correlation between fatigue and hemoglobin level in multiple myeloma patients: Results of a cross-sectional study. *ASH 2002 (abstract 38).*

Prince, H.M., Mileshkin, L., Roberts, A., Ganju, V., Underhill, C., Catalano, J., et al.

(2005). A multicenter phase II trial of thalidomide and celecoxib for patients with relapsed and refractory multiple myeloma. *Clinical Cancer Research, 11*(15), 5504-5514.

Prue, G., Rankin, J., Allen, J., Gracey, J., & Cramp. F. (2006). Cancer-related fatigue: A critical appraisal. *European Journal of Cancer, 42,* 846-863.

Qazilbash, M.H., Saliba, R.M., Hosing, C., Mendoza, F., Qureshi, S.R., Weber, D.M., et al. (2007). Autologous stem cell transplantation is safe and feasible in elderly patients with multiple myeloma. *Bone Marrow Transplantation, 39,* 279-283.

Rajkumar, S.V., Blood, E., Vesole, D., Fonseca, R., & Greipp, P.R. (2006). Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: A clinical trial coordinated by the Easter Cooperative Oncology Group. *Journal of Clinical Oncology, 24,* 431-436.

Rajkumar, S., Hayman, S., Lacy, M., Dispenzieri, A., Hoerin, A., Geyer, S., et al. (2004). Combination therapy with CC-5013 (lenalidomide; Revlimid) plus dexamethasone (Rev/Dex) for newly diagnosed myeloma (MM). *Blood, 104,* 331 (ASH Annual Meeting Abstracts).

Reece, D. (2005). An update of the management of multiple myeloma: The changing landscape. *Hematology,* 353-359.

Reece, D.E., Bredeson, C., Perez, W.S., Jagannath, S., Zhang, M.J., Ballen, KK, et al. (2003). Autologous stem cell transplantation in multiple myeloma patients <60 vs ≥60 years of age. *Bone Marrow Transplantation, 32,* 1135–1143.

Richardson, P.G., Hideshima, T., & Anderson, K.C. (2003). Bortezomib (PS-341): A

novel, first-in-class proteasome inhibitor for the treatment of multiple myeloma and other cancers. *Cancer Control, 10*(5), 361-369.

Rivera, S., Liu, L., Nemeth, E., Gabayan, V., Sorensen, O.E., & Ganz, T. (2005). Hepcidin excess induces the sequestration of iron and exacerbates tumor-associated anemia. *Blood, 105*(4), 1797-1802.

Rosinol, L., Lahuerta, J.J., Sureda, A., de la Rubia, J., Garcia-Larana, J., Hernandez-Garcia, M. et al. (2005). Feasibility and efficacy of a planned second transplant ("auto" or "mini-allo") intensification in patients with multiple myeloma not achieving complete remission (CR) or near-CR with a first autologous transplant: Results from a Spanish PETHEMA/ GEM study [abstract]. *Haematologica, 90*(s1): PL9.05.

Rossi, J.F., Feguex, N., Lu, Z.Y., Legouffe, E., Exbrayat, C., Bozonnat, M.C. et al. (2005). Optimizing the use of anti-interleukin-6 monoclonal antibody with dexamethasone and 140mg/m^2 of melphalan in multiple myeloma: Results of a pilot study including biological aspects. *Bone Marrow Transplantation, 36,* 771-779.

San Miguel, J.F., Almeida, J., & Orfao, A. (2002). Laboratory investigations. In J. Mehta & S. Singhal (Eds.), *Myeloma* (pp. 243-268). London, England: Martin Dunitz Ltd.

Schubert, C., Hong, S., Natarajan, L., Mills, P.J., & Dimsdale, J.E. (2006 in press). The association between fatigue and inflammatory marker levels in cancer patients: A quantitative review. *Brain, Behavior and Immunity.* Retrieved March 27, 2007 from:

http://www.sciencedirect.com.login.ezproxy.library.ualberta.ca/science?_ob=ArticleURL&_udi=B6WC1-4MKV2M2-2&_user=1067472&_coverDate=12%2F18%2F2006&_alid=555491369&_rdoc=1&_fmt=full&_orig=search&_cdi=6725&_sort=d&_docanchor=&view=c&_ct=1&_acct=C000051251&_version=1&_urlVersion=0&_userid=1067472&md5=e2d1a828ee0188306215e8baef5c9e34

Siegel, D.S., Desikan, K.R., Mehta, J., Singhal, S., Fassas, A., Munshi, N., et al. (1999). Age is not a prognostic variable with autotransplants for multiple myeloma. *Blood, 93*(1), 51-54.

Smith, A., Wisloff, F., & Samson, D. (2006). Guidelines on the diagnosis and management of multiple myeloma 2005. *British Journal of Haematology, 132*(4), 410-451.

Sonneveld, P., van der Holt, B., Segeren, C.M., Vellenga, E., Croockevit, A.J., Verhoef, G.E. et al. (2005). Intensive versus double intensive therapy in untreated multiple myeloma: Update analysis of the randomized phase III HOVON 24 study. *Haematologica, 90,* 37PL8.01.

Stasi, R., Abriani, L., Beccaglia, P., Terzoli, E., & Amadori, S. (2003). Cancer-related fatigue. Evolving concepts in evaluation and treatment. *Cancer, 98*(9), 1786-1801.

Stasi, R., Amadori, S., Littlewood, T.J., Terzoli, E., Newland, A.C., & Provan, D. (2005). Management of cancer-related anemia with erythropoietic agents: Doubts, certainties, and concerns. *The Oncologist, 10,* 539-554.

Stead, M.L., Brown, J.M., Velikova, G., Kaasa, S., Wisloff, F, Child, J.A., et al. (1999).

Development of an EORTC questionnaire module to be used in health-related quality-of-life assessment for patients with multiple myeloma. *British Journal of Haematology, 104,* 605-611.

Stone, P.C., Abdul-Wahab, A., Gibson, J.S., Wright, R.J., & Andrews, P.L. (2005). Fatigue in cancer patients is not related to changes in oxyhemoglobin dissociation. *Supportive Care in Cancer, 13*(10), 854-858.

Stone, P., Richards, M., A'Hern, R., & Hardy, J. (2000). A study to investigate the prevalence, severity and correlates of fatigue among patients with cancer in comparison with a control group of volunteers without cancer. *Annals of Oncology, 11*, 561-567.

To, L.B., Haylock, D.N., Simmons, P.J., & Juttner, C.A. (1997). The biology and clinical uses of blood stem cells. *Blood, 89*(7), 2233-2258.

Trikha, M., Corringham, R., Klein, B., & Rossi, J.F. (2003). Targeted anti-interleukin 6 monoclonal antibody therapy for cancer: A review of the rationale and clinical evidence. *Clinical Cancer Research, 9,* 4653-4665.

University of Alberta. (2004). *Human research – University of Alberta standards for the protection of human research participants.* Retrieved August 5, 2004, from: www.ualberta.ca/~unisecr/policy/sec66.html

Van Zaanen, H.C., Lokhorst, H.M., Aarden, L.A., Rensink, H.J., Warnaar, S.O., Van der Lelie, J., et al. (1998). Chimeric anti-interleukin 6 monoclonal antibodies in the treatment of advanced multiple myeloma: A phase I dose escalating study. *British Journal of Haematology, 102*, 783-790.

Wagner, L.I., & Cella, D. (2004). Fatigue and cancer: Causes, prevalence and treatment

approaches. *British Journal of Cancer, 91,* 822-828.

Wang, L.M., Weber, D., Delasalle, K., & Alexanian, R. (2004). VTD (Velcade, thalidomide, dexamethasone) as primary therapy for newly-diagnosed multiple myeloma. *Blood, 104,* 210 (ASH Annual Meeting Abstracts).

Wang, X.S., Giralt, S.A., Mendoza, T.R., Engstrom, M.C., Johnson, B.A., Peterson, N. et al. (2002). Clinical factors associated with cancer-related fatigue in patients being treated for leukemia and non-hodgkin's lymphoma. *Journal of Clinical Oncology, 20*(5), 1319-1328.

Wisloff, F., Eika, S., Hippe, E., Hjorth, M., Holmberg, E., Kaasa, S., et al. (1996). Measurement of health-related quality of life in multiple myeloma. *British Journal of Haematology, 92,* 604-613.

Wisloff, F., Gulbrandsen, N., Hjorth, M., Lenhoff, S., & Fayers, P. (2005). Quality of life may be affected more by disease parameters and response to therapy than by haemoglobin changes. *European Journal of Haematology, 75,* 293-298.

Wisloff, F., & Hjorth, M. (1997). Health-related quality of life assessed before and during chemotherapy predicts for survival in multiple myeloma. *British Journal of Haematology, 97,* 29-37.

Wood, L.J., Nail, L.M., Gilster, A., Winters, K.A., & Elsea, C.R. (2006). Cancer chemotherapy-related symptoms: Evidence to suggest a role for proinflammatory cytokines. *Oncology Nursing Forum, 33*(3), 535-542.

Wratten, C., Kilmurray, J., Nash, S., Seldon, M., Hamilton, C.S., O'Brien, P.C et al.

(2004). Fatigue during breast radiotherapy and its relationship to biological factors. *International Journal of Radiation Oncology, Biology and Physics, 59*(9), 160-167.

Yellen, S.B., Cella, D.F., Webster, K., Blendowski, C., & Kaplan, E. (1997). Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *Journal of Pain and Symptom Management, 13,* 63-74.

Appendix A

Consent Form

CONSENT FORM

TITLE: **Examining the relationships between clinical variables, quality of life and fatigue in patients with multiple myeloma.**

INVESTIGATORS: Reanne Booker, RN BScN MN(c)
Karin Olson, RN PhD

This consent form is only part of the process of informed consent. It should give you the basic idea of what the research is about and what your participation will involve. If you would like more detail about something mentioned here, or information not included here, please ask. Take the time to read this carefully and to understand any accompanying information. You will receive a copy of this form.

BACKGROUND:

Fatigue is one of the most common symptoms people with cancer experience. Even though is it very common, the reasons why someone becomes tired are not well understood.

We want to learn more about why people with cancer become so tired. If we can discover some of the reasons why people experience fatigue, we may be able to treat this symptom more effectively.

This study will use information from your chart, such as your stage of disease and laboratory information and your responses from two questionnaires. The information collected will be analyzed to look for relationships. For example, from previous research studies, we have learned that there is a relationship between hemoglobin level and fatigue.

WHAT IS THE PURPOSE OF THE STUDY?

The purpose of this study is to explore the experience of fatigue in individuals with multiple myeloma. Many people with cancer experience fatigue, or tiredness. This may be the result of the cancer itself. It also may be due to treatment, nutritional changes, weight loss, uncontrolled symptoms (such as nausea or pain) or other reasons.

WHAT WOULD I HAVE TO DO?

Participating in this study will involve:

a) the completion of two questionnaires. Each one takes about 10 minutes each to complete. We would like you to complete these questionnaires at each clinic visit for three cycles of treatment.

b) the collection of information from your chart by study researchers. This may include information such as the results of your blood tests, stage of disease and type of treatment you are on.

WHAT ARE THE RISKS?

There are no risks involved in participating in this study. At any point, you may withdraw from participating.

WILL I BENEFIT IF I TAKE PART?

The possible benefit to you for participating in this study is that you will help researchers understand more about fatigue.

DO I HAVE TO PARTICIPATE?

You do not have to participate in this study. You are free to withdraw from the research study at any time. This will not affect your continuing medical care in any way.

WILL MY RECORDS BE KEPT PRIVATE?

Personal records relating to this study will be kept confidential. Any research data collected about you during this study will not identify you by name. Only your initials and a coded number will be used. Your name will not be disclosed outside the research clinic. Any report published as a result of this study will not identify you by name.

The health information collected as part of this study will be kept confidential unless release is required by law. It will be used only for the purpose of the research study. Only the study investigators (Dr. K. Olson and Ms. R. Booker) will have access to information collected in the study.
All data will be kept in a secure environment in the office of Ms. Booker at the Tom Baker Cancer Center.

SIGNATURES

Your signature on this form indicates that you have understood to your satisfaction the information regarding your participation in the research project and agree to participate as a subject. In no way does this waive your legal rights nor release the investigators, or involved institutions from their legal and professional responsibilities. You are free to withdraw from the study at any time without jeopardizing your health care. If you have further questions concerning matters related to this research, please contact:

Dr. Karin Olson (780) 492-6403

or

Ms. Reanne Booker (403) 521-3906

If you have any questions concerning your rights as a possible participant in this research, please contact Pat Evans, Associate Director, Internal Awards, Research Services, University of Calgary, at 220-3782.

Participant's Name	Signature and Date
Investigator/Delegate's Name	Signature and Date
Witness' Name	Signature and Date

The University of Calgary Conjoint Health Research Ethics Board has approved this research study.
A signed copy of this consent form has been given to you to keep for your records and reference.

Appendix B
Study Instruments

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____

Your birthdate (Day, Month, Year): _____

Today's date (Day, Month, Year): 31 _____

		Not at All	A Little	Quite a Bit	Very Much
1	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2	Do you have any trouble taking a long walk?	1	2	3	4
3	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4	Do you need to stay in bed or a chair during the day?	1	2	3	4
5	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6	Were you limited in doing either your work or other daily activities?	1	2	3	4
7	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8	Were you short of breath?	1	2	3	4
9	Have you had pain?	1	2	3	4
10	Did you need to rest?	1	2	3	4
11	Have you had trouble sleeping?	1	2	3	4
12	Have you felt weak?	1	2	3	4
13	Have you lacked appetite?	1	2	3	4
14	Have you felt nauseated?	1	2	3	4
15	Have you vomited?	1	2	3	4
16	Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

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EORTC QLQ - MY24

Patients sometimes report that they have the following symptoms. Please indicate the extent to which you have experienced these symptoms during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Have you had bone aches or pain?	1	2	3	4
32. Have you had pain in your back?	1	2	3	4
33. Have you had pain in your hip?	1	2	3	4
34. Have you had pain in your arm or shoulder?	1	2	3	4
35. Have you had pain in your chest?	1	2	3	4
36. If you had pain did it increase with activity?	1	2	3	4
37. Did you feel drowsy?	1	2	3	4
38. Did you feel thirsty?	1	2	3	4
39. Have you felt ill?	1	2	3	4
40. Have you had a dry mouth?	1	2	3	4
41. Have you lost any hair?	1	2	3	4
42. Answer this question only if you lost any hair:				
Were you upset by the loss of your hair?	1	2	3	4
43. Did you have tingling hands or feet?	1	2	3	4
44. Did you feel restless or agitated?	1	2	3	4
45. Have you had acid indigestion or heartburn?	1	2	3	4
46. Have you had burning or sore eyes?	1	2	3	4

Please turn to next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
47. Were you satisfied with your relationship with your doctors?	1	2	3	4
48. Were you satisfied with the care you received from your doctors?	1	2	3	4
49. Were you satisfied with the information you received about your illness?	1	2	3	4
50. Did you feel that you were being listened to by your doctor/nurse?	1	2	3	4
51. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
52. Have you been thinking about your illness?	1	2	3	4
53. Have you been worried about dying?	1	2	3	4
54. Have you worried about your health in the future?	1	2	3	4

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FACIT-Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI 12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An 12	I am too tired to eat	0	1	2	3	4
An 14	I need help doing my usual activities	0	1	2	3	4
An 15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An 16	I have to limit my social activity because I am tired	0	1	2	3	4

US English
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